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PULMONARY (VENOUS) AIR EMBOLISM

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ALTHOUGH pulmonary air embolism is relatively infrequent in medical practice, it is so catastrophic when it does occur that further investigation into its etiology, pathologic physiology, prophylaxis, and treatment is fully warranted. Moreover, as recently emphasized by Martland,[1] its importance, from the standpoint of frequency, may be much greater than has been recognized, since very few of these accidents are likely to be reported, and, in other instances in which an autopsy is not done, death may be attributed erroneously to heart disease or some other condition.

DIFFERENTIATION OF PULMONARY AND ARTERIAL AIR EMBOLISM

Basic to an understanding of pulmonary (venous) air embolism is a clear conception of its differentiation from the arterial form of air embolism. Although both depend for their effects on the presence of air in the circulation, the site of entrance of the air determines its distribution within the vascular system and is therefore extremely important. In the pulmonary form, air enters one of the systemic veins and is carried to the right heart and pulmonary circulation and depends for its effects upon mechanical obstruction of the outflow tract of the right ventricle as will be explained subsequently. Fairly large amounts of air are needed to produce this effect. In arterial embolism, on the other hand, the air gains entrance to the pulmonary venous channels and is propelled from the left ventricle to those systemic arteries which supply the superiorly located

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portions of the body. Since a small amount of air can effectively block a medium-sized artery, serious consequences may result when a few cubic centimeters of air enter the pulmonary vein and are carried into either the coronary, or cerebral circulation, or both. Our studies[2] have shown that as little as 0.025 c.c. of air injected directly into the anterior descending branch of the left coronary artery of a dog can produce an ischemic disturbance in the myocardium supplied by that artery, and an increase of the amount injected to as much only as 0.05 c.c. may cause death of the animal.

As would be expected from what has already been said, the clinical picture in the two forms of embolism is totally different. In the pulmonary, or venous form, the presence of air in the right ventricle produces a loud, churning sound, often readily heard without stethoscopic aid, which is known as the "millwheel" murmur. This murmur appears almost immediately after air has entered the venous circulation. As a result of the obstruction of the right ventricular outflow tract from the air trap which forms within it, the venous pressure rises to a marked degree, and cyanosis becomes readily apparent. Associated with these retrograde circulatory effects, there also appear the manifestations of forward circulatory failure, namely, a falling blood pressure, a rapid thready pulse, and syncope due to cerebral ischemia. As will be explained later, we have discovered in our experiments that all of these manifestations are profoundly influenced by position of the body.

In the arterial form, the clinical picture is dependent upon ischemia in vital organs, especially the heart and brain. If the head is higher than the level of the arch of the aorta, air will enter the cerebral circulation and cause various neurological manifestations, such as aphasia, blindness, hemiplegia, or monoplegia. Examination of the fundus oculi may be of great diagnostic value in such cases since air bubbles may be observed in the retinal vessels.[3] Of further diagnostic value is the observation of a marbled appearance of the skin indicating involvement of the superficial vessels. The demonstration of "air bleeding" which can be accomplished by making a small incision in the skin over the most superior portion of the body is conclusive evidence of this form of air embolism.[4] Involvement of the coronary arteries is probably an important factor in causing death in these cases. Myocardial infarction has been demonstrated by electrocardiography,[5] and post-mortem and experimental evidence have also shown the importance of involvement of these vital arteries.[6-9]

The position of the body is much less important therapeutically in arterial air embolism than in the pulmonary form. The head down position does *prevent* cerebral involvement if the patient is in that position when the embolism occurs, but it does not cause a clearing of the cerebral manifestations if the position is assumed only *after* the accident has taken place. Furthermore, it does not prevent coronary artery involvement.

A summary of these differences between pulmonary and arterial air embolism is presented in Table I. Subsequent discussion in this paper will deal entirely with *pulmonary* air embolism.

TABLE I. DIFFERENTIATION OF PULMONARY (VENOUS) AND ARTERIAL AIR EMBOLISM

	PULMONARY	ARTERIAL
Site of entrance of air	Peripheral veins	Pulmonary veins
Procedures responsible	Surgical Obstetrical Diagnostic or therapeutic air insufflation	Thoracentesis Pneumothorax Thoracic surgery
Fatal dose of air	Large	Small
Cause of death	Air trap– Pulmonary conus	Cerebral embolism Coronary embolism
Favorable position	Left lateral	Head down
Signs	Mill wheel murmur Increased venous pressure	Air bleeding Fundus examination Marbled skin
Blood pressure	Lowered	Elevated (initially)

ETIOLOGY OF PULMONARY AIR EMBOLISM

Air may enter the systemic veins in sufficient quantity to produce serious embolic manifestations under a number of different circumstances.[10] These may be summarized as follows:

A. Surgical
   1. Operations involving veins of neck
   2. Operations involving dural sinuses
   3. Uterine curettage

B. Diagnostic air injections
   1. Into the perirenal area
   2. Into the peritoneal cavity
      a. Direct
      b. Transuterine (Rubin test)
   3. Into the urinary bladder
   4. Into the joints

C. Therapeutic air injections
   1. Maxillary antrum lavage
   2. Pneumoperitoneum
   3. Vaginal insufflation by powder blowers

D. Obstetrical
   1. During delivery of patients with placenta previa

E. Accidental entrance of air into intravenous apparatus
   (This accident is rare)

A detailed analysis of each of these circumstances is unnecessary, but several of them deserve additional emphasis. It is of especial interest to note that the injection of air into the perirenal area, a procedure which is admittedly of great value in the diagnosis of adrenal tumors, has been abandoned in many clinics because of the frequency with which air embolism occurs during this procedure despite careful technique. Another fact worth noting is that, of all the veins of the body, the uterine sinuses are probably the most vulnerable to the entrance of air, a circumstance which makes obstetrics and gynecology the specialties in which this complication is most to be feared. A particularly impressive demonstration of this vulnerability is provided by the recently reported deaths from air embolism which have resulted from the simple procedure of vaginal insufflation for trichomonas infestation.[11-14] This has occurred especially when the treatment has been used during pregnancy, but it has also been observed in nonpregnant individuals near the time of menstruation.

EXPERIMENTAL STUDIES

The studies to be reported in this communication were carried out in order to obtain more complete information than has heretofore been available concerning the mechanism of death in pulmonary air embolism and to attempt to discover means of preventing this occurrence. Not only have the studies fulfilled this purpose, but they have also provided information of great interest concerning electrocardiographic changes associated with acute right ventricular dilatation and with ischemia involving the right ventricular musculature.

Experimental Procedure.—The dog was used as the experimental animal. Sodium pentothal, 20 mg. per kilogram of body weight, and sodium barbital, 150 mg. per kilogram of body weight, were administered intravenously for anesthesia. Ten animals received air injections into the femoral vein with the thorax intact, standard electrocardiograms being taken before and at intervals after the injection. In ten other animals, which were given artificial respiration, the thorax was opened by a sternum-splitting incision and direct observation of cardiac changes was made following the injections of air into the femoral vein. In seven of these, electrocardiograms were taken by means of a direct lead from the right ventricular muscle adjacent to the anterior descending branch of the left coronary artery. This electrode was paired with one attached to the left hind leg. In three animals leads from the right ventricular cavity were obtained. The use of a cardioscope permitted constant observation of the electrocardiographic changes, and film recordings were taken as indicated.

Following the completion of the experiment, careful autopsy study was made to determine the distribution of the air in those animals in which the thorax was intact.

OBSERVATIONS

Experiments With Intact Thorax.—Following the injection of from 25 to 150 c.c. of air into the femoral vein, a gallop rhythm and a loud millwheel murmur which was audible without a stethescope were heard over the precordium. Tachy-

cardia, marked tachypnea, cyanosis, and elevation of the venous pressure were then noted. Whether or not fatality occurred depended on factors to be discussed later. Several animals tolerated repeated injections of as much as 100 c.c. of air at intervals of five to ten minutes.

Experiments With Open Thorax.—Observation of the heart through a sternum-splitting incision in ten experiments showed an extremely interesting succession of events following the femoral air injection. The same millwheel murmur was heard as in the experiments in which the thoraces were intact. Tachypnea was, of course, not observed, since the animals were receiving artificial respiration. Almost immediately following the injection of air, there was noted a sudden marked dilatation of the right auricle and ventricle associated with the rise in venous pressure which had been observed in the intact thorax experiments. With the marked dilatation of the right ventricle, which was especially profound in the outflow tract region, there developed an area of readily observed ischemia just to the right of the lower reaches of the anterior descending branch of the left coronary artery. This ischemic region is shown as a shaded area in the drawing (Fig. 1) made from a photograph of one of the animal hearts. The most ventral

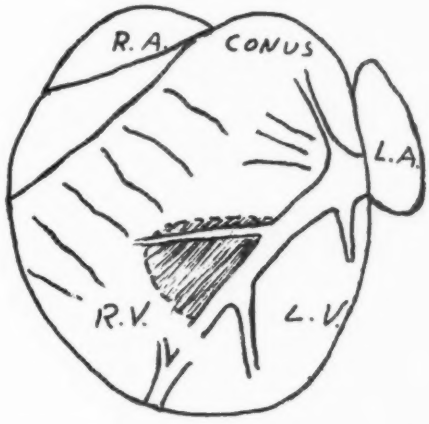

Fig. 1.—Drawing made from photograph of dog's heart showing area of ischemia (shaded area) located to the right of the anterior descending branch of the left coronary artery.

portion of the right ventricular outflow tract was found by transillumination to contain a large air bubble. In these open chest experiments, survival was much less likely, and, even with relatively small amounts of air (25 to 50 c.c.), the right ventricular dilatation continued and the contractions became more and more feeble until death supervened. If, however, the animal was turned onto his left side before the dilatation had become extreme, the contractions of the right ventricle again became strong and the animal recovered. This remarkable recovery from seemingly irreversible right ventricular failure was associated with disappearance of the large air bubble previously present in the region of the pulmonary conus and artery, these regions no longer being superiorly located with respect to the other portions of the right ventricle.

FACTORS INVOLVED IN FATALITY IN EXPERIMENTAL PULMONARY AIR EMBOLISM

No attempt was made in these experiments to determine the fatal dosage of air in relationship to body weight, as has been done by others.[15] Our experience has been that the dosage which will produce fatality is extremely unpredictable, and, while there is undoubtedly some relationship to the size of the animal, many other factors are involved which greatly complicate any attempt at calculation. It is our belief that the cross-sectional area of the right ventricular outflow tract at its most superior point, (this point will depend upon the position of the animal) is probably much more closely related to the fatal dosage than is the weight of the animal.

The factors which we have found to be most closely related to mortality can be summarized as follows:

1. *The amount of air injected.* As already stated, this is undoubtedly a very important factor, but it is so modified by others as to make the calculations of a dosage/weight relationship for all circumstances an impossibility.

2. *The speed of the injection.* We have found that tremendous quantities of air can be injected without fatality if sufficient time is taken for the injection. Thus, one animal survived a total of 1,000 c.c. of air which was injected in amounts of 100 c.c. at intervals of five to ten minutes. Not all animals, however, will tolerate such a procedure.

3. *The position of the animal.* This is a tremendously important factor, we believe, and one which has not been mentioned in any of the previous studies of this subject. We have found that an animal can tolerate more air when lying on his left side than can be tolerated in any other position. Furthermore, if an animal is allowed to develop evidence of marked right ventricular failure while lying on his back, and is then turned onto the left side, recovery frequently follows immediately. As we have already pointed out, the return of forceful right ventricular contractions under these circumstances is dramatic. Conversely, the right lateral position is by far the worst position of all for the animal. It is of interest that tachypnea does not occur when the animal is in this latter position.

An explanation for the recovery of animals when turned into the left lateral position is to be found in the observations made in the open chest experiments. These have shown that the right ventricle labors against the obstruction of an air trap in its outflow tract when the position of the animal is such as to make this the most superior portion of the right heart. Such would be the case with the animal on his back or on his right side. When turned onto the left side, however, the outflow tract assumes a position inferior to the body of the right ventricle. The air trap then disappears from this, now inferior, position and is presumably churned into a froth which is mixed with the blood in the right ventricular cavity. The obstruction to the circulation is thus relieved and blood can be propelled into the pulmonary vessels by the now unimpeded right ventricular contractions. The froth gradually disappears from the cavity of the right ventricle, and it must be assumed that it has been transported into the lungs with the blood where excretion can take place.

4. *The effectiveness of the pulmonary excretory mechanism.* As previously explained, tachypnea failed to occur under two circumstances in our experiments. It was absent in the intact thorax experiments when the animal was on his right side, and it was absent in the open chest experiments with artificial respiration. It was under these two conditions that the smallest amounts of air were found to be fatal. It would seem, then, that the tachypnea ordinarily present with air embolism acts in some manner as a protective mechanism and tends to prevent death.

Cause of the Myocardial Ischemia.—The ischemia of the right ventricular musculature which was noted in the open chest experiments requires reference to the work of Visscher[16] for its explanation. This investigator has shown that the flow of coronary blood depends on a pressure gradient measured by the differences in pressure between the aorta at one end of the coronary circuit and the coronary sinus and right ventricle at the other end. Furthermore, the *relative* amount of blood flow to the coronary sinus and to the right ventricle (thru the thebesian channels) is determined by the aorta-pulmonary artery pressure difference. The greater this pressure difference, the greater the thebesian flow and the less the coronary sinus flow. With a low aorta-pulmonary artery pressure difference there will be a great falling off of the thebesian flow. Since the right ventricular muscle is particularly dependent upon the blood which traverses the coronary-thebesian circuit for its nourishment, it is the right ventricle which is especially vulnerable to increased pressure in its outflow tract, in contrast to the left ventricle which can tolerate increased loads for long periods of time. When the pressure within the right ventricular cavity is markedly increased, as in our air embolism experiments, the thebesian flow is greatly restricted. At the same time, there is a reduction in the aortic pressure, and these two factors combine to reduce markedly the aortic-right ventricular pressure gradient so that blood flow to the muscle of the right ventricle is impaired and gives rise to ischemia. Why this ischemia is grossly evident in only one part of the right ventricular muscle we are unable to determine at the present time.

ELECTROCARDIOGRAPHIC CHANGES

The standard electrocardiogram in the ten closed thorax experiments demonstrated striking alterations at the time when the circulatory disturbances were at their height. These consisted in marked depressions of the S-T segments in Leads II and III without complete obliteration of the upright T waves (Fig. 2). No change in the S-T segment in Lead I was noted. Disturbances in rhythm, consisting in varying degrees of A-V block or the development of nodal rhythm, were not infrequent. The deviation of the S-T segments disappeared rapidly when recovery from the embolic disturbance occurred.

In the ten open chest experiments, the opportunity was afforded to lead directly from the area of ischemia previously described and outlined in Fig. 1. This was done in seven experiments and an invariable sequence of marked changes occurred. These changes are shown in tracings from a representative experiment (Fig. 3). It will be seen that, almost immediately following the

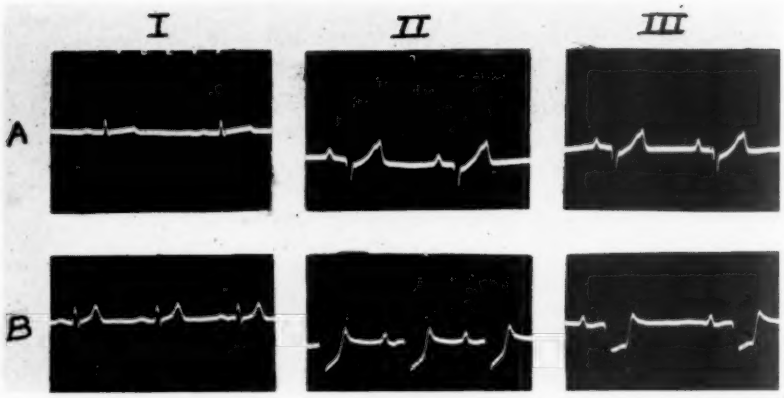

Fig. 2.—Standard electrocardiograms in closed thorax experiment before (*A*) and after (*B*) the injection of 100 c.c. of air into the femoral vein of a dog. Marked changes in S-T segments in Leads II and III are shown in *B*.

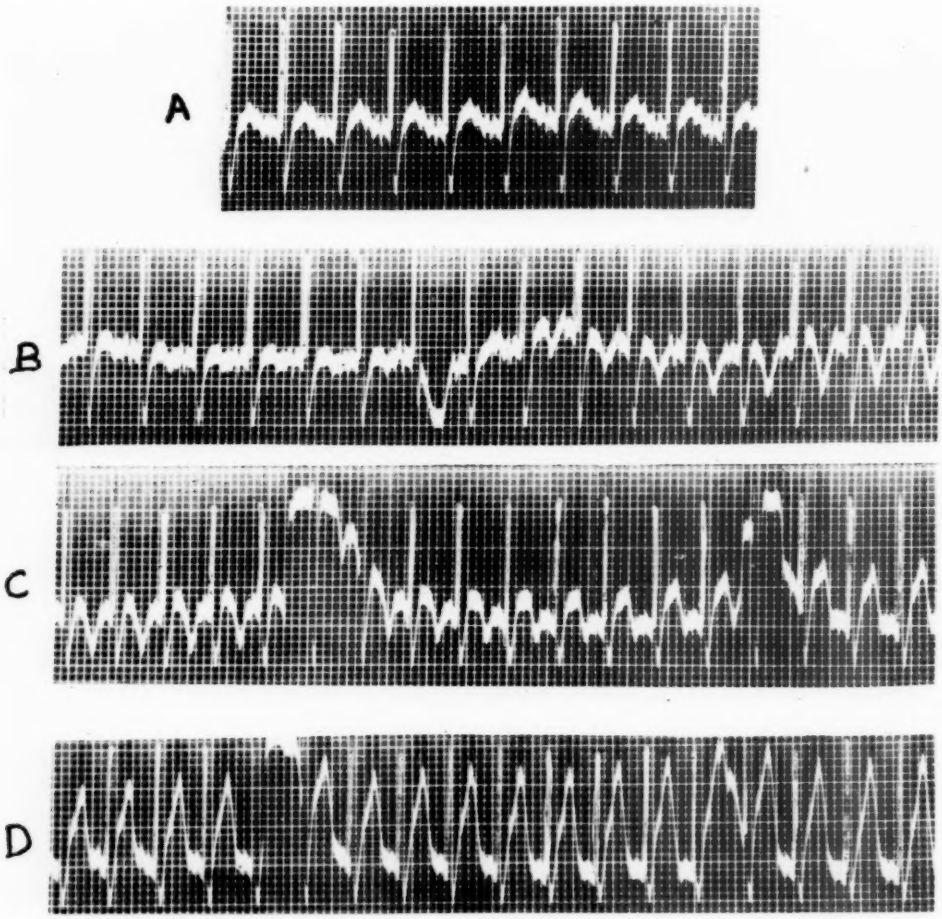

Fig. 3.—Open thorax experiment. Exploring electrode on ischemic area. Indifferent electrode on left hind leg. Positivity of exploring electrode represented by upstroke. Appearance and disappearance of ischemia-injury pattern well shown.

A: Control, thorax open. *B:* Immediately after the injection of 30 c.c. of air. *C:* Ten seconds after the end of *B*. *D:* Immediately after *C*. *E:* Sixteen seconds after *D*. *F:* Twenty-one seconds after *E*. *G:* Dog turned onto left side. Sixty-six seconds after *F*. *H:* Following recovery. T waves subsequently became upright. (The R waves have been retouched in this figure.)

injection of air, sharp inversion of the T wave takes place (Fig. 3, *B*). Ten seconds later (Fig. 3, *C*), an elevation of the S-T segment makes its appearance and, as it gradually becomes more marked, the T-wave inversion disappears. There then develops a more and more extreme S-T segment deviation. When this attains a maximum (Fig. 3, *F*), elevation of the S-T segment considerably

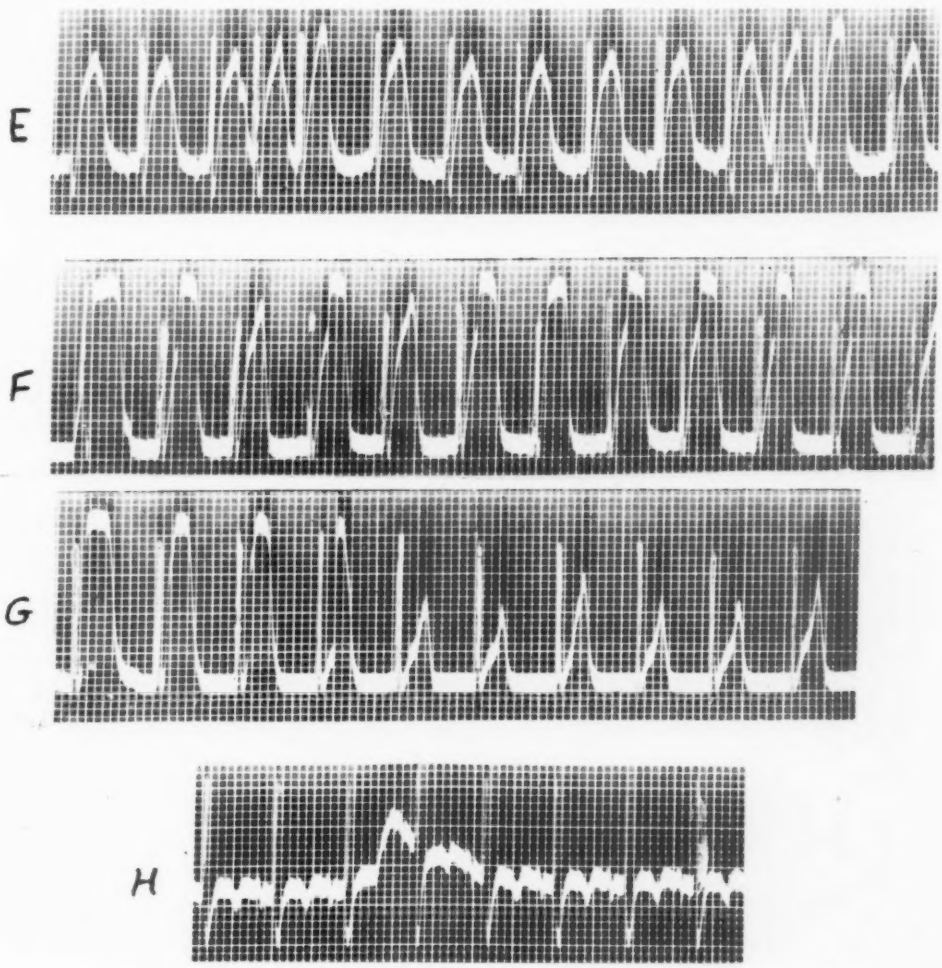

Fig. 3 (Cont'd).—*For complete legend, see opposite page.*

surpasses the R wave in height. There is also some change in the QRS complex which consists in the disappearance of the normal S wave. When the animal was turned onto his left side in this experiment, the previously noted changes disappeared rapidly in the reverse order (Fig. 3, *G*). In tracings that followed those shown in Fig. 3, *H*, there was a return of the normal upright T wave.

The sequence of changes described is identical with that observed by Bayley and LaDue[17] in studies of the ischemia-injury pattern induced by subtotal,

temporary occlusion of a coronary artery. In their studies, as in ours, inversion of the T waves (first stage ischemia) preceded the appearance of S-T segment deviation (second stage ischemia-current of injury phase). Bayley and LaDue were not able, however, to obtain as complete a reversal of changes as occurred in these experiments.

In addition to the changes in the final ventricular deflection which have been described, marked alterations in the QRS complex were observed in three experiments. An example of these changes is shown in Fig. 4. The same sequence

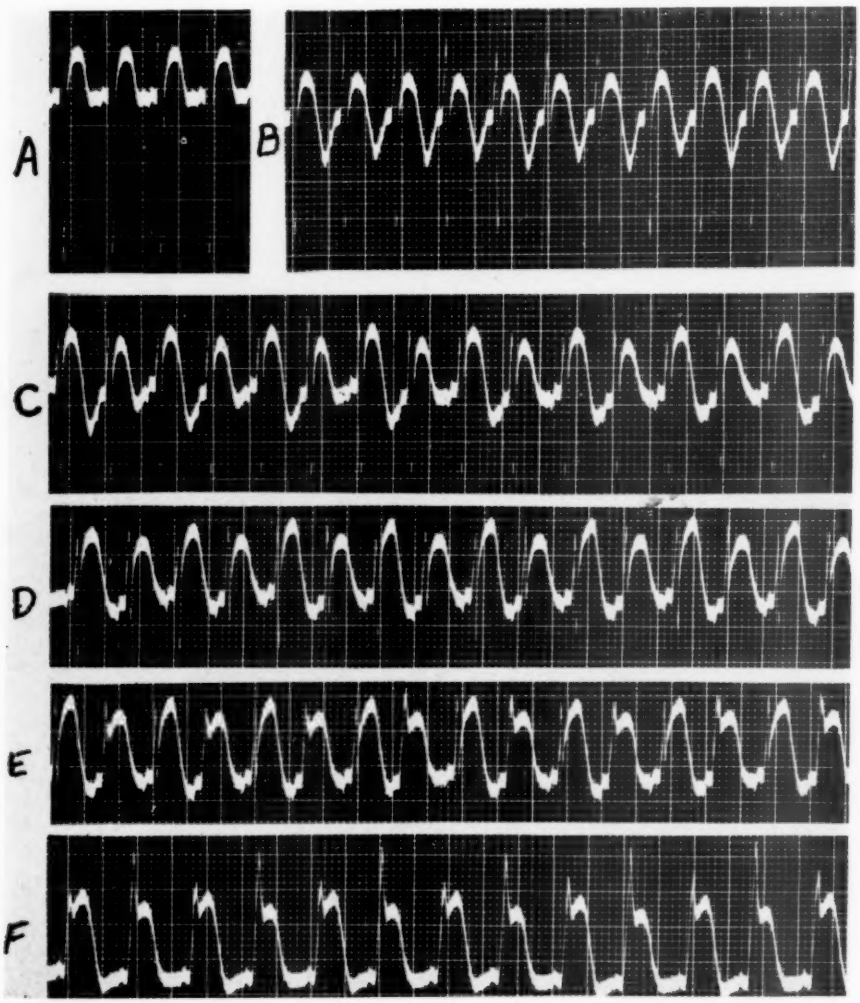

Fig. 4.—Open thorax experiment. Same technique as in Fig. 3. Demonstrates gradual development of right ventricular conduction defect.

A: **Control, thorax open.** *B:* **Immediately after the injection of 30 c.c. of air.** *C:* **Immediately following** *B.* *D:* **Twenty seconds after** *C.* *E:* **Ten seconds after** *D.* *F:* **Forty-five seconds after** *E.* **For description of changes see text.**

of events involves the S-T segment, the T waves, and the ischemia-injury pattern that are shown in Fig. 3. The animal was not allowed to recover, however, so there is no reversal of these changes. With reference to the QRS complex, the same gradual disappearance of the S wave is observed, and, during the progress of this disappearance, an electrical alternans occurs in which there is a reciprocal relationship between the depth of the S wave and the height of R. When the disappearance of the S wave has become complete (Fig. 4, *E*), there is seen to be a notching of R, or a second positive upstroke in the QRS complex. In the last tracing (Fig. 4, *F*), the height of the R wave has considerably increased, and there is also increased width. Thus, there is observed the development of considerable delay in complete activation of the musculature subjacent to the electrode, since the activating impulse is still travelling toward the electrode at the end of ventricular excitation, whereas in the control tracing (Fig. 4, *A*) the activation of the subjacent musculature was complete at a time when much of the remainder of the myocardium had yet to be activated (as indicated by the large S wave).

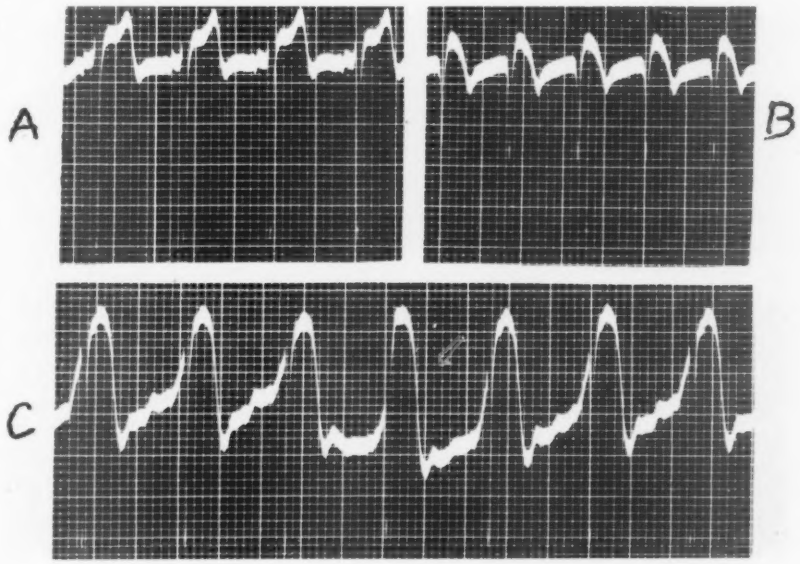

Fig. 5.—Open thorax experiment. Exploring electrode leading from right ventricular cavity. Indifferent electrode on left hind leg.

A: Control. Electrode within right ventricular cavity. *B:* After injection of 30 c.c. of air. Early ischemia pattern well shown by T-wave inversion. *C:* Two minutes after *B*. Large broad initial upstroke now present in QRS complex.

In order to determine whether or not the delay in activation of the right ventricular muscle under the electrode was due to a septal effect, three experiments were performed using an electrode within the cavity of the right ventricle according to the method of Wilson and co-workers.[18] The results of these experiments were similar and are represented by the tracings shown in Fig. 5. The control tracing (Fig. 5, *A*) shows a very small initial upward deflection, as is

often the case normally within the right ventricle, due presumably to a slightly later activation of the right side of the ventricular septum than of the left. Following air embolism (Fig. 5, *B*), T-wave inversion is again noted, followed by S-T segment elevation (Fig. 5, *C*), exactly as in leads from the epicardial surface of the heart. The striking feature of the tracing shown in Fig. 5, *C*, however, is the appearance of a large, broad upstroke at the beginning of the initial ventricular defiection. The possibility that this finding represents the development of right bundle branch block must be seriously considered. This is of especial interest since acute dilatation of the right ventricle in man, due to solid pulmonary emboli (acute cor pulmonale), has been shown to produce temporary right bundle branch block in some instances.[19]

SUMMARY

Pulmonary (venous) air embolism is a catastrophe which may occur under a variety of circumstances in medical practice. It must be distinguished from arterial air embolism. Our studies in the experimental animal have shown that important factors in determining whether death or survival will occur are: (1) the amount of air which gains admission to the circulation, (2) the speed with which it enters, (3) the position of the body at the time of the embolic accident, and (4) the efficacy of the respiratory excretory mechanism. Death, when it occurs, is due to circulatory obstruction resulting from an air trap in the right ventricular outflow tract. Displacement of the air trap by turning the body into the left lateral position may be life saving even after the right ventricular contractions have become feeble and death seems imminent.

Pulmonary air embolism provides a valuable means of studying experimentally the effects of acute right ventricular dilatation produced by obstruction. The rapid and profound electrocardiographic changes which occur under these circumstances include an excellent demonstration of the effects of myocardial ischemia, and also, in some instances, the demonstration of right ventricular conduction defects. The observations of Bayley and LaDue concerning the ischemia-injury pattern are confirmed.

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THE HEART IN UREMIA

An Electrocardiographic and Pathologic Study

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PATIENTS with uremia tend to show marked changes in the electrocardiogram. The role of the uremic intoxication in the genesis of these alterations is difficult to determine since uremia is usually the terminal phase of a long-lasting and progressive disease which affects the heart muscle and gives rise to various electrocardiographic changes long before the uremic changes set in. During the past decade we have become more familiar with the electrocardiographic patterns resulting from these conditions preceding or concomitant with uremia and thus are able to evaluate the factors that determine the final changes during the uremic stage. We are familiar with (1) the different patterns of chronic left heart strain and its improved and simplified diagnosis by multiple chest leads,[1] (2) the electrocardiographic patterns associated with disease of the coronary arteries, (3) the changes produced by diffuse pericarditis, and (4) the changes seen in acute glomerulonephritis; finally, (5) we have learned to recognize the effect on the electrocardiogram of hypocalcemia and hyperpotassemia. Bearing in mind the complexity of the problem, an attempt was made to study the electrocardiographic changes in a group of uremic patients who came to autopsy and to correlate the electrocardiographic with the pathologic findings. The study of the pathologic changes of the myocardium was considered to be important not only in relation to the electrocardiogram, but also in view of the paucity and discordance of previous reports on the pathologic cardiac changes in uremia.

MATERIAL AND METHOD

With the exception of two cases (Cases 26 and 27), the twenty-seven cases studied (Table I) were consecutive necropsied cases with a clinical diagnosis of uremia and with one or more electrocardiograms taken during the uremic stage. The last electrocardiogram in these patients was taken anywhere from eight weeks to less than twenty-four hours ante mortem. In thirteen, only a single record

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was taken and, in the remaining ones, from two to seventeen records taken over a period of from ten days to fourteen years were available. A complete autopsy was performed in all cases and numerous sections were taken from different parts of the myocardium, fixed in formalin, and stained with hematoxylin and eosin. sudan III stain for fat was used in about one-half of the cases. In every instance where pericarditis was present, particular attention was paid to the adjacent myocardium.

The electrocardiograms were analyzed objectively, without knowledge of the autopsy findings, and the abnormalities listed (Table I); in every case the record was specifically examined for evidence of left heart strain (chronic left ventricular strain), myocardial infarction, pericarditis, hypocalcemia, and hyperpotassemia. Then electrocardiographic interpretation and anatomic findings were compared to determine the extent of agreement. Discrepancies were specifically noted.

CLINICAL FINDINGS

The clinical data are summarized in Table I. Twenty of the twenty-seven patients in this series were men and seven were women. Most patients were between 40 and 60 years of age; the average age was 47 years.

The nonprotein nitrogen ranged between 57 and 300 mg. per 100 c.c. of blood (with an average of 135) and was above 90 mg. per 100 c.c. in all but three patients. In the three exceptions it was slightly below that level but was rapidly rising and was associated with other unmistakable signs of uremia. The creatinine level was often determined and was always elevated. The systolic arterial blood pressure ranged between 135 and 260 mm. Hg (with an average of 194 mm.). The diastolic pressure was elevated in all but six instances. Many patients presented a severe hypochromic anemia with a red blood corpuscle count as low as 2 million per cubic millimeter and a hemoglobin reduced to as much as 30 per cent of normal. Calcium was determined in nine patients and showed a level of less than 9.0 mg. per 100 c.c. in five instances (averaging 8.5 mg.). No potassium determinations were carried out except in one patient (Case 27) where a value of 24 mg. per cent was obtained. Many of the chemical determinations were carried out long before death, and it can be presumed that more marked variations from the normal took place in many instances during the last days of life. This is especially true since several patients in our series showed a progressively increasing oliguria and often a terminal anuria.

PATHOLOGIC FINDINGS

The basic renal lesions are listed in Table II. There were four cases of arteriolonecrosis of the kidneys, two of them associated with arteriolosclerosis, one with chronic glomerulonephritis, and one with chronic pyelonephritis.

The average weight of the heart was 466 grams, the minimum weight was 300 grams, and the maximum weight was 650 grams. There was no definite relation between the weight of the heart and the underlying renal disease. More consistently high weights, however, were found in nephrosclerosis of the arteriolar

TABLE

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	CORONARY ARTERIOSCLEROSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
1	M 52	Enlarged prostate; cystotomy; phlebitis; angina pectoris; acute suppurative cystitis	Hb., —; R.B.C., —; N.P.N., 108; B.P., 136/92	Acute pyelonephritis with abscesses	350	0.4	1.2	Normal	Slight hypertrophy and fibrosis; old and organizing infarcts (I.V. septum); fat infiltration of right ventricle	+
2	M 56	Chronic glomerulonephritis; hypertensive heart disease; acute bronchopneumonia	Hb., 75%; R.B.C., 3.79; N.P.N., 86; B.P., 150/120	Nephrosclerosis of the arteriolar variety	525	0.4	1.3	Normal	Hypertrophy; moderate interstitial fibrosis; dilatation of chambers with mural thrombi	+
3	M 57	Chronic pyelonephritis and nephrolithiasis; hypertensive heart disease with failure	Hb., 55%; R.B.C., 2.3; N.P.N., 240; B.P., 180/90; Ca, 6.1	Pyelonephritic contracted kidneys; nephrolithiasis	500	0.4	1.6	Acute serofibrinous pericarditis with extension into the myocardium	Moderate hypertrophy; severe interstitial fibrosis, more marked in the outer third of the ventricular wall; slight endocardial fibrosis	+++
4	M 46	Hypertensive cardiorenal disease; acute bronchopneumonia	Hb., 50%; R.B.C., 3.33; N.P.N., >74; B.P., 220/110	Arteriolosclerosis and necrosis	500	0.6	1.8	Acute fibrinous pericarditis with extension into the myocardium	Slight hypertrophy and fibrosis	++
5	M 62	Hypertensive cardiorenal disease; acute bronchopneumonia; pulmonary infarcts; prostatism	Hb., 70%; R.B.C., 3.95; N.P.N., 92; B.P., 184/130	Pyelonephritic contracted kidneys	650	0.7	2.0	Normal	Marked hypertrophy and interstitial fibrosis; old and recent infarcts of the anterior and posterior walls of the left ventricle and of the posterior wall of the right ventricle	+++

Coronary arteriosclerosis: +, slight; + +, moderate; + + +, severe, with or without occlusion.
R.V.W.: Thickness of right ventricular wall.
L.V.W.: Thickness of left ventricular wall.
I.V. block: Intraventricular block.

I

NUMBER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							ECG AND NECROPSY AGREEMENT	FIG.
				HYPOCALCEMIA	HYPERPOTASSEMIA	CHRONIC LEFT VENTRICULAR STRAIN	MYOCARDIAL INFARCT	PERICARDITIS	NONSPECIFIC ABNORMALITY	NOTE		
1	10/8/37		10/23/37	—	—		+	—		I.V. block (S type)	No discrepancy	
3	1/22/38	2/2/38	2/2/38	+	—			+			No pericarditis at autopsy	
2	9/8/38	10/17/38	10/19/38	+	—			?	+	I.V. block (Indeterminate)	No discrepancy	
1	9/2/39		9/4/39	—	—		—	—	+	I.V. block (Indeterminate)	Pericarditis at autopsy	
5	3/22/40	5/20/40	6/14/40	—	—		—	—	+	I.V. block (Common type)	Old (and recent) infarct at autopsy	

TABLE I

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	CORONARY ARTERIOSCLEROSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
6	M 69	Prostatectomy; postoperative progressive acute uremia; bronchopneumonia	Hb., 40%; R.B.C., 2.3; N.P.N., 110; B.P., 152/72	Acute pyelonephritis with abscesses	—	0.3	1.0	Old fibroadhesive and recent serohemorrhagic pericarditis with extension into the myocardium	Slight interstitial and perivascular fibrosis	+
7	F 57	Hypertensive heart disease with failure; marked oliguria; acute bronchopneumonia	Hb., 30%; R.B.C., 2.5; N.P.N., 98; B.P., 220/40	Pyelonephritic contracted kidneys with nephrosclerosis	460	0.5	1.5	Petechial hemorrhages over right auricle	Moderate hypertrophy and slight fibrosis	++
8	F 50	Chronic glomerulonephritis; oliguria; anuria during last 24 hours; acute bronchopneumonia	Hb., 30%; R.B.C., 2.46; N.P.N., 144; B.P., 135/90	Pyelonephritic contracted kidneys	300	0.2	1.1	Normal	Slight hypertrophy; moderate interstitial fibrosis	+
9	M 34	Hypertensive heart disease; pulmonary edema	Hb., 50%; R.B.C., 2.28; N.P.N., 124; B.P., 190/120; Ca, 9.6	Subchronic glomerulonephritis; arterial nephrosclerosis	475	0.5	1.5	Normal	Marked hypertrophy; interstitial and perivascular fibrosis; old anterior wall infarct with aneurysmal dilatation	+++
10	M 49	Malignant nephrosclerosis; urea frost; syphilitic aortitis; acute bronchopneumonia	Hb., 70%; R.B.C., 4.5; N.P.N., 152; B.P., 260/114; Ca, 10	Arteriolosclerosis and necrosis of the kidneys; acute pyelonephritis	500	0.6	2.5	Acute serofibrinous pericarditis with extension into the myocardium	Marked hypertrophy, moderate interstitial and perivascular fibrosis	++
11	M 63	Malignant nephrosclerosis; hypertensive heart disease; acute bronchopneumonia	Hb., —; R.B.C., —; N.P.N., 120; B.P., 196/106	Chronic pyelonephritis	650	0.3	1.7	Acute fibrinous pericarditis; old adhesions	Moderate hypertrophy; slight interstitial fibrosis; old infarct of the left ventricle (apex)	+++

CONT'D

NUMBER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							EGG AND NECROPSY AGREEMENT	FIG.
				HYPOCALCEMIA	HYPERPOTASSEMIA	CHRONIC LEFT VENTRICULAR STRAIN	MYOCARDIAL INFARCT	PERICARDITIS	NONSPECIFIC ABNORMALITY	NOTE		
3	7/13/40	7/23/40	7/23/40	—	—	—	—	—	+		Pericarditis at autopsy	
1	9/27/40		10/16/40	+	+	+	—	—			No discrepancy	
1	10/21/40		10/30/40	++	—	—	—	—	+		No discrepancy	
1	10/22/40		11/15/40	—	—		+	—			No discrepancy	
2	10/10/40	11/15/40	11/18/40	+	—		—	+		Left ventricular strain obscured by pericarditis	No discrepancy	1
9	9/30/40	4/12/41	5/2/41	—	—	?	?	—	+	Combined heart strain ?	No discrepancy	

TABLE I

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	CORONARY ARTERIOSCLEROSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
12	M 79	Hypertrophy of the prostate; ascending pyelonephritis; acute bronchopneumonia	Hb., 50%; R.B.C., 2.9; N.P.N., 157; B.P., 150/100	Chronic pyelonephritis	450	0.2	1.2	Normal	Slight hypertrophy	+
13	F 15	Hydronephrosis with malignant hypertension and heart failure	Hb., 40%; R.B.C., 1.8; N.P.N., 118; B.P., 230/160	Chronic pyelonephritis with bilateral hydronephrosis; arteriolonecrosis	400	0.4	1.2	Normal	Moderate hypertrophy; slight interstitial and perivascular fibrosis	0
14	M 65	Nephrosclerosis with hypertensive heart disease; acute bronchopneumonia	Hb., 87%; R.B.C., 4.67; N.P.N., 118; B.P., 180/98; Ca, 11.0	Arteriolosclerosis; acute glomerulonephritis	425	0.4	1.5	Normal	Moderate hypertrophy; slight interstitial and perivascular fibrosis; acute myocarditis	+
15	F 55	Old nephrectomy; chronic renal disease with heart failure	Hb., 49%; R.B.C., 3.2; N.P.N., 152; B.P., 160/88	Chronic pyelonephritis	400	0.4	1.2	Normal	Moderate hypertrophy and interstitial fibrosis; old and recent infarcts of the left ventricle (apex)	+++
16	M 26	Chronic glomerulonephritis; hypertensive heart disease with failure	Hb., 36%; R.B.C., 2.0; N.P.N., 154; B.P., 200/130; Ca, 8.1	Chronic pyelonephritis; proliferative glomerulonephritis	400	0.4	1.3	Acute pericarditis (partial)	Slight hypertrophy; slight interstitial and perivascular fibrosis	++
17	F 42	Chronic glomerulonephritis; hypertensive heart disease with failure; pulmonary edema	Hb., 43%; R.B.C., 2.50; N.P.N., 171; B.P., 195/110	Chronic glomerulonephritis	425	0.3	1.0	Acute fibrinous pericarditis with extension into the myocardium	Moderate hypertrophy and interstitial fibrosis; fat infiltration of right ventricle	++

CONT'D

NUMBER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							ECG AND NECROPSY AGREEMENT	FIG.
				HYPOCALCEMIA	HYPERPOTASSEMIA	CHRONIC LEFT VENTRICULAR STRAIN	MYOCARDIAL INFARCT	PERICARDITIS	NONSPECIFIC ABNORMALITY	NOTE		
1	4/12/41		5/22/41	—	—	+	—	—			No discrepancy	
5	5/20/40	10/13/41	12/1/41	+	++	+	—	—			No discrepancy	
1	4/15/42		4/20/42	—	—	+	—	—			No discrepancy	
1	6/16/42		7/8/42	—	—	+	—	—			Old (and recent) infarct at autopsy	
1	7/10/42		8/6/42	++	—	?	—	?	+	Combined heart strain ?	No discrepancy	
5	6/15/38	8/8/42	8/13/42	++	++		—	?		Left ventricular strain obscured by K changes	No discrepancy	2

TABLE I

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	CORONARY ARTERIOSCLEROSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
18	M 50	Arteriosclerotic heart disease with uremia; urea frost; oliguria; acute bronchopneumonia	Hb., 54%; R.B.C., 3.88; N.P.N., 120; B.P., 260/150; Ca, 9.5	Old pyelonephritis; arteriolosclerosis of the kidneys	500	0.4	1.6	Normal	Moderate interstitial and perivascular fibrosis, especially marked in the outer third; moderate hypertrophy	++
19	F 24	Tuberculous osteomyelitis; pregnancy; chronic glomerulonephritis with uremia and terminal anuria	Hb., 45%; R.B.C., 3.26; N.P.N., 224; B.P., 220/158; Ca, 7.8	Amyloidotic contracted kidneys	475	0.4	2.1	Acute and organizing fibrinohemorrhagic pericarditis	Moderate hypertrophy; moderate interstitial and perivascular fibrosis	+
20	F 44	Malignant nephrosclerosis; uremia; progressive oliguria; acute bronchopneumonia	Hb., 60%; R.B.C., 3.38; N.P.N., 155; B.P., 210/140	Subacute glomerulonephritis and arteriolonecrosis	400	—	—	Acute fibrinous pericarditis	Moderate fibrosis and hypertrophy	++
21	M 28	Hypertensive cardiorenal disease with oliguria; multiple pulmonary infarcts	Hb., 54%; R.B.C., 2.49; N.P.N., 100; B.P., 210/35	Subacute glomerulonephritis and arteriolonecrosis	500	0.3	1.8	Minimal lymphocytic infiltration	Moderate to severe hypertrophy and fibrosis; some fatty degeneration; mural thrombi in right auricle	++
22	M 58	Hypertensive cardiovascular disease; hydrothorax	Hb., 60%; R.B.C., 3.60; N.P.N., 112; B.P., 210/140	Polycystic kidneys	475	0.7	1.9	Normal	Moderate hypertrophy and fibrosis; old infarct of anterior wall of left ventricle and interventricular septum; moderate endocardial thickening	+++

CONT'D

NUMBER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							EGG AND NECROPSY AGREEMENT	FIG.
				HYPOCALCEMIA	HYPERPOTASSEMIA	CHRONIC LEFT VENTRICULAR STRAIN	MYOCARDIAL INFARCT	PERICARDITIS	NONSPECIFIC ABNORMALITY	NOTE		
1	8/13/42		8/24/42	—	—	+	—	—			No discrepancy	
5	2/11/42	11/3/42	11/4/42	+	—	+	—	+			No discrepancy	
2	12/17/42	5/14/43	5/28/43	++	—	+	—	—		Combined heart strain	No discrepancy	
1	6/28/43		8/25/43	++	—	+	—	—		Combined heart strain	No discrepancy	
17	6/21/33	7/30/43	9/21/43	—	—	?	+	—		Combined heart strain?	No discrepancy	

TABLE I

CASE	SEX AGE	CLINICAL INFORMATION	LABORATORY DATA	RENAL PATHOLOGY	HEART			PERICARDIUM	MYOCARDIUM AND ENDOCARDIUM	CORONARY ARTERIOSCLEROSIS
					WT. (GM.)	R.V.W. (CM.)	L.V.W. (CM.)			
23	F 52	Hypertensive heart disease; nephrosclerosis; uremia	Hb., 52%; R.B.C., 3.05; N.P.N., 94; B.P., 220/120	Nephrosclerosis of the arteriolar variety	550	0.4	1.8	Normal	Severe diffuse fibrosis and hypertrophy; multiple small infarcts of right and left ventricles	+++
24	F 22	Chronic glomerulonephritis with moderate oliguria and uremia; severe anemia	Hb., 25%; R.B.C., 1.60; N.P.N., 300; B.P., 175/135	Subchronic glomerulonephritis	375	0.3	1.8	Normal	Slight interstitial fibrosis and hypertrophy; moderate fatty degeneration; fat infiltration of the right ventricle	++
25	M 28	Chronic glomerulonephritis; hypertension; acute bronchopneumonia	Hb., 53%; R.B.C., 3.89; N.P.N., 125; B.P., 180/100; Ca, 8.8	Acute pyelonephritis superimposed on chronic pyelonephritic contracted kidneys	525	0.5	1.8	Acute fibrinous pericarditis	Moderate hypertrophy; slight interstitial fibrosis; severe cloudy swelling; acute endocarditis of mitral valve	+
26	M 62	Nephrolithiasis; chronic pyelonephritis; marked oliguria with terminal anuria; acute bronchopneumonia	Hb., 43%; R.B.C., 2.50; N.P.N., 116; B.P., 160/110	Pyelonephritic contraction of left kidney; compensatory hypertrophy and arteriosclerosis of right kidney	400	0.5	1.5	Acute serofibrinous hemorrhagic pericarditis	Moderate hypertrophy and interstitial fibrosis	++
27	M 51	Hypertensive heart disease; diabetes mellitus; intracapillary glomerulosclerosis	Hb., 39%; R.B.C., 2.1; N.P.N., 200; B.P., 200/100; Ca, 6.2; K, 24	Pyelonephritic contracted kidneys	600	0.8	2.3	Organized fibroadhesive pericarditis; few small hemorrhages	Marked hypertrophy; moderate interstitial fibrosis; some cloudy swelling; moderate sclerotic thickening of mitral and aortic valves	++

CONT'D

NUMBER OF ECG'S	FIRST ECG	LAST ECG	DEATH	ELECTROCARDIOGRAPHIC DIAGNOSIS							EGG AND NECROPSY AGREEMENT	FIG.
				HYPOCALCEMIA	HYPERPOTASSEMIA	CHRONIC LEFT VENTRICULAR STRAIN	MYOCARDIAL INFARCT	PERICARDITIS	NONSPECIFIC ABNORMALITY	NOTE		
1	9/27/43		9/27/43	—	—	+	—	—			Small infarcts at autopsy	
1	10/13/43		10/24/43	++	+		—	—			No discrepancy	
8	7/10/29	11/26/43	12/8/43	+	+	+	—	—			No discrepancy	
3	3/21/44	4/24/44	4/24/44	—	++		—	—		Left ventricular strain obscured by K changes; I.V. block (S type); A-V block	No discrepancy	4
7	4/6/42	9/2/45	9/8/45	++	+	+	—	—			No discrepancy	3

TABLE II

Acute ascending pyelonephritis	2
Chronic pyelonephritis	13
Subacute and chronic glomerulonephritis	5
Nephrosclerosis of the arteriolar variety	5
Amyloid contracted kidneys	1
Polycystic kidneys	1

variety, while approximately normal weights were present in two instances of acute ascending pyelonephritis. Both ventricles were proportionally equally affected by the hypertrophic process. Acute diffuse fibrinous pericarditis was present in eleven (41 per cent) instances. The average nonprotein nitrogen level in these patients was slightly higher (149 mg. per 100 c.c.) than in the others, but no definite relationship could be established between these two findings. Often urea frost on the skin was seen in patients who did not present pericarditis. The pericarditis was generally recent, evidence of an early organization being present in three instances. In six hearts there was a definite extension of the inflammatory process from the pericardium into the superficial layers of the myocardium. However, it is possible that a larger number of sections would have shown involvement of the myocardium in a higher percentage of cases (Fig. 5). The only instance of diffuse myocarditis in our series was not associated with pericarditis and probably was the consequence of an acute bronchopneumonia. In most cases of pericarditis, degeneration of the muscle fibers was more marked in the superficial than in the deeper layers of the myocardium. When pericarditis was absent, this localization of the major degenerative changes could not be observed.

The myocardium was generally rather pale with a moderate to severe cloudy swelling. The consistency was diminished in only a few instances and occasionally edema was present. Old and recent myocardial infarcts were observed in seven hearts, most frequently in the anterior wall of the left ventricle. Microscopically, the most consistent finding in the myocardium was a moderate to severe interstitial fibrosis which was present in the hearts of all but two patients. Both of these patients had acute uremia. In a few instances the myocardial fibrosis was particularly marked in perivascular location. In others either the outer or the inner third of the left ventricular wall was more severely involved. A diffuse, slight fatty degeneration was noted in many hearts. In only two instances, however, did it reach a severe degree; both of these patients had a marked anemia. Fat infiltration of the right ventricular wall was present in eight hearts; the infiltration was rather marked in three.

The mural and valvular endocardium was essentially normal. Ocasionally mural thrombi, subendocardial hemorrhages, and endocardial thickening were found. The coronary arteries presented a moderate to severe arteriosclerosis in all cases. This was particularly true in the extramural branches, while the intramural arteries, as a rule, presented less severe changes. In all instances of renal arteriolosclerosis and arteriolonecrosis, similar changes in the heart were

carefully looked for. We were unable to find necrosis of the myocardial arterioles in any of the four instances in which such change occurred in the kidney. Arteriolosclerosis was frequently present although never in the same degree as in the kidney. Endothelial hyperplasia of the small arteries was also noted in a few instances.

ELECTROCARDIOGRAPHIC FINDINGS

Left Heart Strain.—Evidence of left heart strain in the last electrocardiogram was present in twelve patients; in three other patients the diagnosis had been made in a previous record but was obscured in the last record by changes produced by

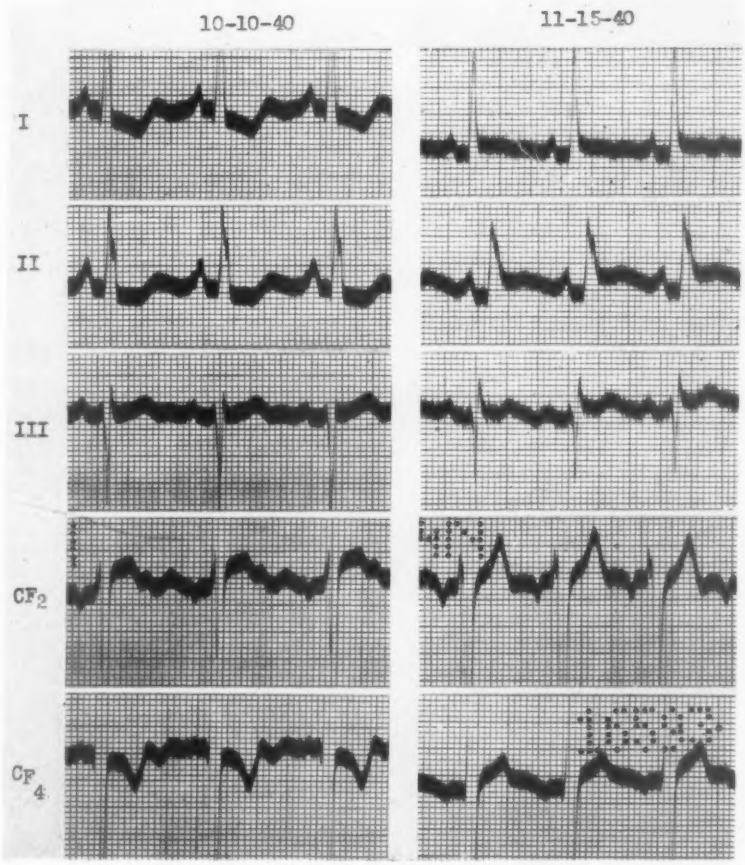


Fig. 1.—Case 10. The record taken Oct. 10, 1940, is characteristic of chronic left heart strain. The typical S-T depression in Leads I and II is replaced by an S-T elevation in the tracing made Nov. 15, 1940; this is ascribed to the effect of acute diffuse pericarditis.

hyperpotassemia (Figs. 2 and 4 and Table I, Cases 17 and 26) or by pericarditis (Fig. 1, Case 10). Of the remaining twelve patients, seven showed changes in all available records which may have masked the pattern of left heart strain. The

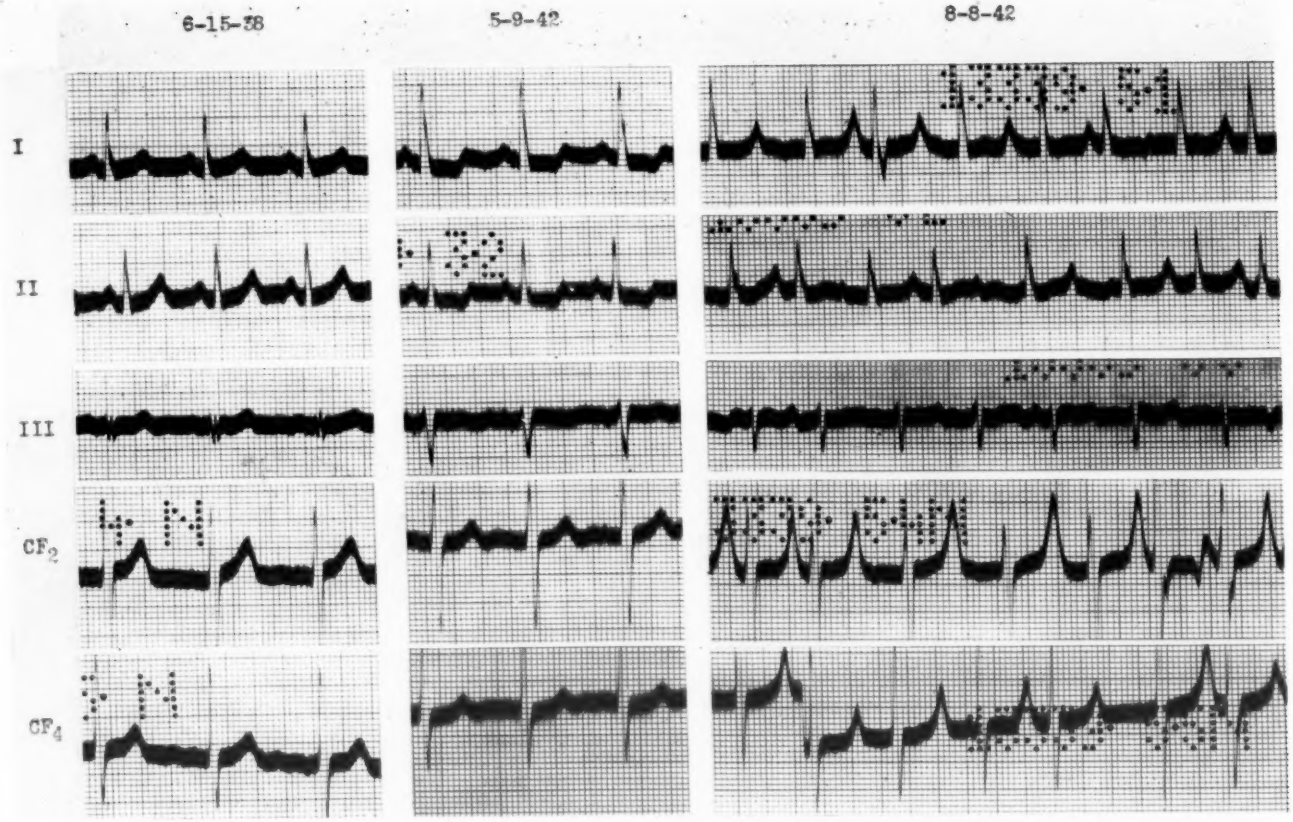


Fig. 2.—Case 17. A normal left axis shift (June 15, 1938) is changed to the pattern of chronic left heart strain (May 9, 1942) and, finally, when uremia develops (Aug. 8, 1942), changes due to hypocalcemia (prolonged electrical systole) and to hyperpotassemia (tall and narrow T waves) appear: sinus rhythm is replaced by auricular fibrillation. Note how the potassium changes obscure the pattern of left heart strain. There are premature ventricular systoles in the last record.

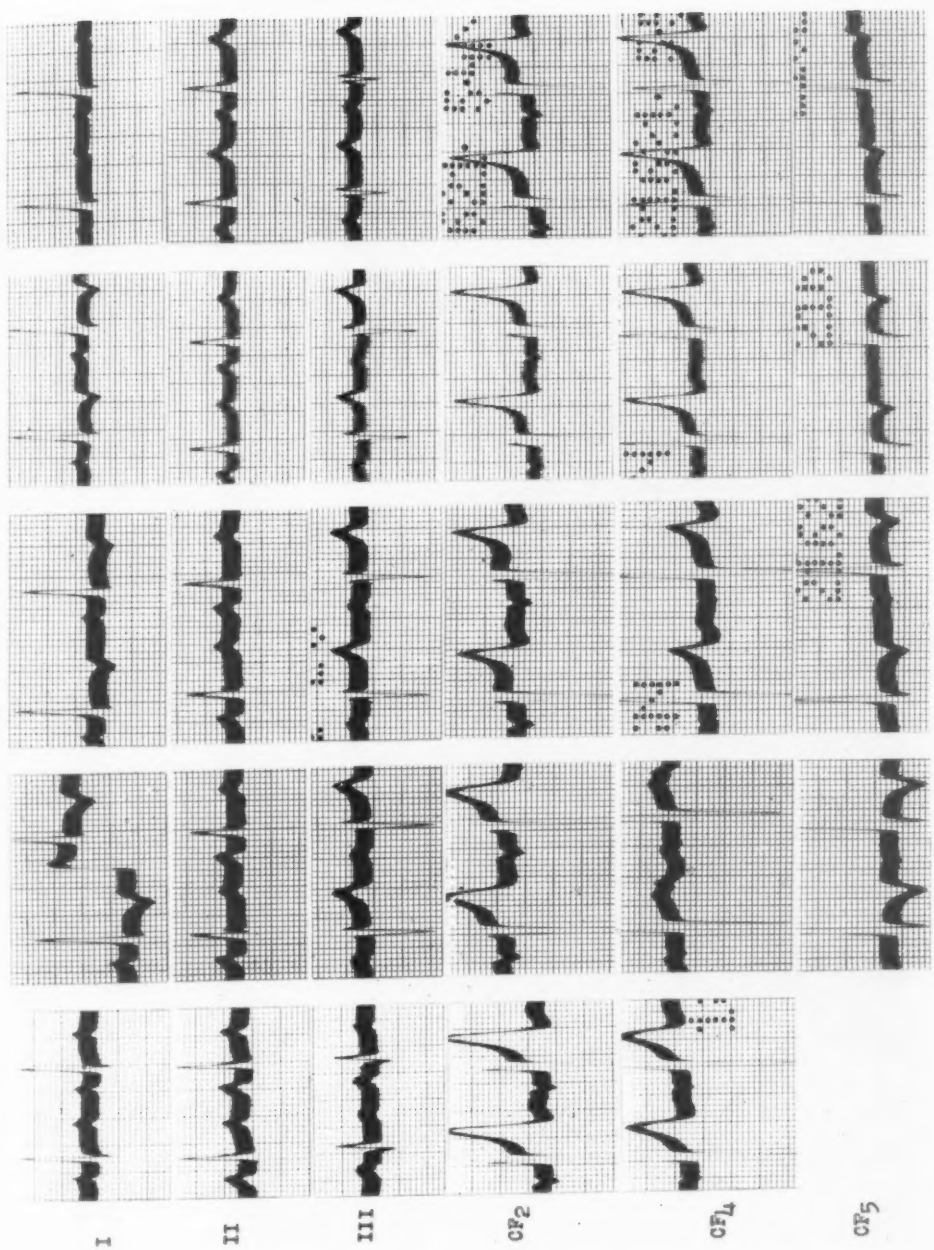


Fig. 3.—Case 27. Note the development of the pattern of left heart strain (Feb. 4, 1944), the evidence of hypocalcemia (prolonged electrical systole) (June 26, 1945), and, finally (June 30, 1945), the appearance of the tall and narrow T wave indicative of hyperpotassemia. Note the potassium effect on the inverted T of left heart strain in Leads I and CF_5 (Sept. 2, 1945).

masking changes consisted of a myocardial infarction pattern in two instances, a pericarditis pattern in one, and intraventricular block in four. In the remaining five cases, nonspecific S-T and T-wave changes were present; in two of this last group the possibility of combined right and left ventricular strain[1,2] was con-

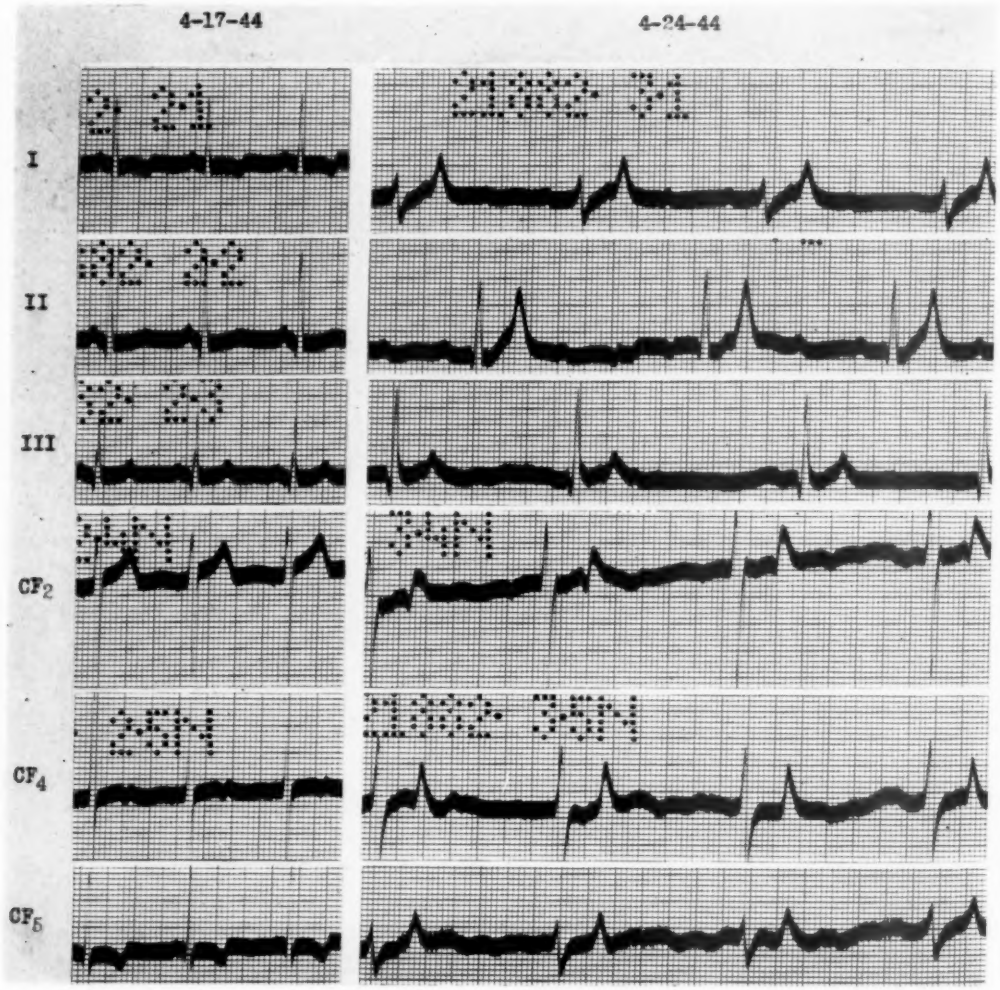


Fig. 4.—Case 26. Effect of uremia on the pattern of "concordant" left heart strain (April 17, 1944). A record taken less than twenty-four hours before death (April 24, 1944) shows second degree A-V block (varying between 4:1 and 3:1), intraventricular block, and tall and narrow T waves.

sidered. In the entire group there was no discrepancy between the electrocardiographic findings and the findings at autopsy, inasmuch as there was no instance where hypertrophy was diagnosed and not found at autopsy and no instance of hypertophy found post mortem where one of the factors just mentioned did not explain the lack of evidence in the electrocardiogram. Nevertheless,

if chest lead CF_5 had been available in all cases, our accuracy in diagnosing left heart strain might have been enhanced.

Myocardial Infarction.—Myocardial infarction was diagnosed in three patients. In two, this lesion was interpreted as being a recent one; in one patient an old lesion was suspected and confirmed by necropsy. Autopsy revealed old myocardial infarcts in three additional patients, two of whom also showed recent infarcts which occurred after the last electrocardiogram had been obtained.

Pericarditis.—Pericarditis with spread to the adjacent myocardium was correctly diagnosed in two patients and suspected and confirmed by autopsy in three other patients. In two additional patients acute pericarditis with spread to the myocardium found post mortem was not reflected in the electrocardiogram. Finally, in one instance T-wave inversions in all limb leads led to the diagnosis of subacute pericarditis which was not confirmed by autopsy.

Hypocalcemia.—The duration of the electrical systole[3] was measured and compared with the value obtained according to the formula $S = 0.39\sqrt{C} \pm 0.04$ second.[3,b] As pointed out by Hegglin and Holzman,[3,b] prolongation of the electrical systole due to hypocalcemia is characterized by prolongation of the S-T segment without broadening of T; this becomes even more obvious when T is abnormally narrow as a result of hyperpotassemia. The electrical systole was prolonged in fourteen patients, in seven of them exceeding the upper limit of the expected value by 0.01 to 0.04 second (listed as + in Table I), and in seven patients, by 0.05 to 0.11 second (listed as ++ in Table I). Such prolongation of the electrical systole was observed in records taken two and one-half years to one day before death. In all but one patient (Case 10) in whom the serum calcium level was determined, the diagnosis of hypocalcemia (less than 10 mg. per cent) was confirmed.

Hyperpotassemia.—Changes ascribed to hyperpotassemia were observed in seven patients. They consisted of changes in T-wave contour in six cases and, in addition, A-V and intraventricular block in one case. The changes are identical with those reported in the literature in experimental potassium poisoning and hyperpotassemia in man which will be reviewed later. The T-wave changes were always of a concordant type, T becoming tall and narrow in the three limb leads and also in the chest leads. In several such instances, previous records were available and showed the profound alteration of an abnormal pre-existing pattern as a result of potassium poisoning (Figs. 2, 3, and 4 and Cases 17, 26, and 27 in Table I); thus, the inverted T of chronic left heart strain was gradually replaced by the upright potassium T wave (Fig. 2, Case 17). The potassium changes were found chiefly in patients with severe oliguria; however, in two patients (Cases 13 and 27) they were observed as early as six and nine weeks before death. T-wave changes characteristic of potassium poisoning were associated with prolongation of the electrical systole in all but one instance (Case 26), and the latter change was found to precede the potassium changes in all instances where earlier records were available. Determination of the serum potassium was

available only in Case 27, but the conditions of the occurrence of the characteristic electrocardiographic changes and their identical appearance with findings reported in established hyperpotassemia justify our interpretation.

Nonspecific Abnormalities.—Nonspecific abnormalities were present in four patients; in two instances in records taken three weeks before death, in the others in records taken two days and one day before death. Three other cases with nonspecific contour changes showed a prolonged electrical systole characteristic of hypocalcemia.

DISCUSSION

Pathologic Findings.—While the pathologic changes in the pericardium in uremia have been well known for a long time, there are only a few reports concerning changes in the myocardium. Bright and others recognized the existence of such changes, but their real nature was not further investigated until recently in connection with electrocardiographic observations.

Lüscher[4.a] described a severe hemorrhagic myocarditis associated with fibrinous pericarditis in a patient with typical uremia. He believed that there was a uremic myocarditis. Richter and O'Hare,[4.b] in analyzing the cardiac findings in chronic glomerulonephritis and especially in uremia, concluded that the heart in this condition is essentially the same as in primary vascular hypertension except for the modification brought about by the lower average age, by the duration of the hypertensive process, by the degree of hypertension, and by the terminal uremic pericarditis. Pericarditis was present in 48 per cent of their series, while the myocardial changes were considered unimportant and nontypical. Gouley,[4.c] on analyzing the hearts of thirty-four patients with uremia, noted a flesh-colored mottling of the muscle with foci of yellowish-gray myocardial degeneration most frequently located in the subepicardial layer of the myocardium. Histologically the main changes observed were fatty and hyaline degeneration with marked swelling of the myocardial fibers; little or no cellular infiltration was found. The fatty degeneration was more marked in the subepicardial layers. Pericarditis was present in 22 per cent of the cases, and since it was not seen in the absence of myocardial degeneration, it was considered to be secondary to the myocardial changes. While rejecting the term uremic myocarditis as improper, Gouley believes in the existence of a specific uremic myocardiopathy. Saphir[4.d] found only five of 240 cases of myocarditis associated with acute or chronic glomerulonephritis or uremia per se. He did not consider the myocardial changes typical for uremia but considered them to be similar to the changes found in any wasting or chronic infectious disease. The vascular changes were similar to those observed in the kidneys in arteriolosclerosis and arteriolonecrosis. Solomon and associates[4.e] were unable to demonstrate any lesion characteristic of the uremic state in the hearts of fifty patients who died in uremia. An unusual endothelial hyperplasia of the cardiac arterioles was present in seven of eight patients with acute necrotizing arteriolitis of the kidneys, but in no other type of renal pathology was there any correlation with the cardiac changes. Other microscopic changes observed were a diffuse fatty degeneration,

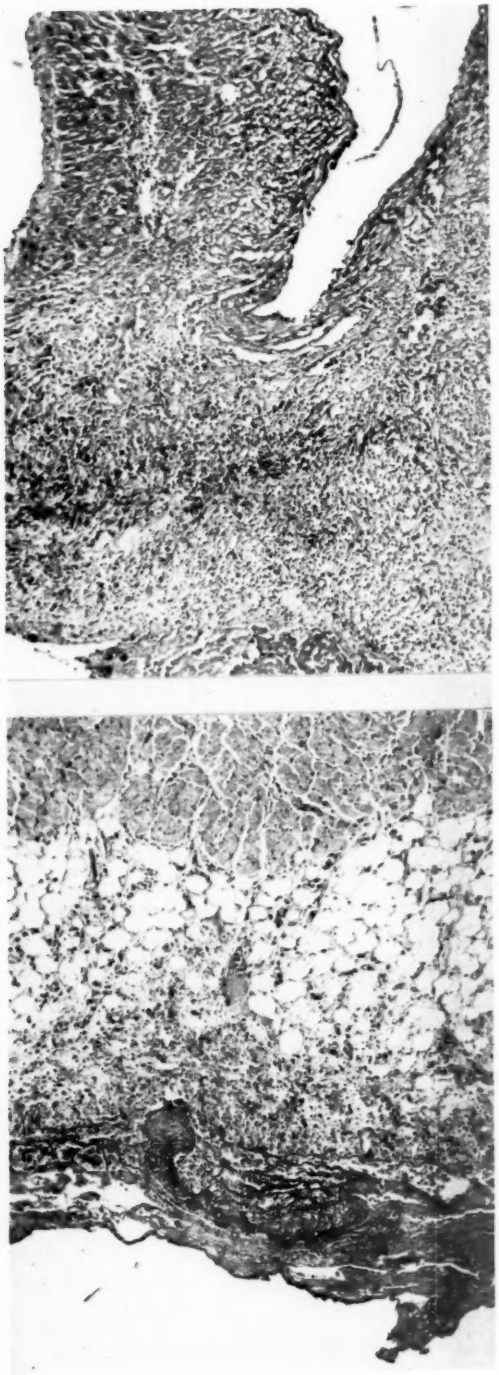
miliary myocardial necrosis, acute interstitial myocarditis (thirty-one cases), and acute miliary infarctions. Either acute or chronic pericarditis was present in 36 per cent of their cases. Winternitz and co-workers[4,f] described anatomic changes in the heart following experimental ligation of both renal arteries in the dog. Edema, hemorrhages, and necroses were noted both in the myocardium and in the small branches of the coronary arteries. However, the production of acute uremia in animals is not comparable with the condition in man where the uremic process progresses slowly over a period of months.

Analysis of the pathologic findings in our series confirms the generally accepted view that if pericarditis is excluded, there are no demonstrable characteristic anatomic changes of the heart in uremia. The hypertrophy of the heart and the interstitial fibrosis of the myocardium are evidently due to the arterial hypertension and to the associated arteriosclerotic process, respectively. The relative rarity of a severe sclerotic process in the intramural coronary arterioles may be due to the fact that the extravascular support of the myocardium acts to protect the smaller intramural arteries from the injurious effect of the elevated arterial blood pressure. Endothelial hyperplasia of the small arteries was neither as frequent nor as typical as reported by Solomon, Roberts, and Lisa.[4,e] Pericarditis frequently extended into the superficial layers of the myocardium and this is important in relation to the electrocardiographic changes. The fatty degeneration of the myocardial fibers, often severe, is certainly not specific. This degeneration, when present, is most likely due to the severe anemia exhibited by these patients. We were unable to confirm the findings of Gouley concerning the subepicardial localization of the degenerative changes.

The severe cloudy swelling and the occasional edema of the myocardium can, of course, be considered to be due to the profoundly altered physiochemical changes and to the modification of the electrolyte balance known to occur in the tissues in uremia. Certain metabolites known to increase in the serum have been demonstrated to be present in increased amounts in the heart muscle.[5]

The changes of the calcium and potassium contents of the blood must be emphasized. They have a direct effect on the myocardial fiber and determine typical changes in the electrocardiogram. In uremia, especially when it is the result of chronic glomerulonephritis, there is a diminution of the calcium content in the blood (hypocalcemia) because of retention of phosphates.[6] The increase of potassium in body fluids (hyperpotassemia) which occurs in uremia results from the breakdown of body cells and the inability on the part of the body to excrete the potassium by any channel other than the kidney or to store any considerable amount.[7]

In marked experimental hyperpotassemia produced in dogs, Hall and Cleghorn[8] demonstrated changes in the heart which consisted grossly of petechial hemorrhages and microscopically of changes in the small and medium-sized arteries. These showed desquamation of endothelial cells, occasional thrombosis with occasional organization, degeneration of the media, and edema of the arterial wall. In a few instances in our series where the electrocardiogram showed evidence of hyperpotassemia, a careful search revealed no lesions attributable to retained potassium. This is in accordance with the findings of Keith and co-workers.[9]



B.

A.

Fig. 5.—Two cases of uremic pericarditis. Sections through the outer layer of the ventricular wall. *A*. Pericarditis limited to the epicardium. Note the abundant fibrinous exudate and the lymphocytic and mononuclear infiltration of the subepicardial fat tissue. *B*. Pericarditis with extension into the myocardium. The inflammatory cells extend deeply into the myocardium.

Electrocardiographic Findings.—Of the various changes encountered in electrocardiograms taken in patients with uremia, primarily those ascribed to hyperpotassemia need further discussion. A brief review of the recent advances in this subject will clarify our problem.

In 1938 Winkler, Hoff, and Smith[10·a] observed a characteristic sequence in the electrocardiogram of the dog after intravenous injection of potassium similar to that previously described by Wiggers[10·b] and others. The same sequence of electrocardiographic changes was observed in 1940 by Winternitz and associates[4·f] and in 1941 by Hoff, Smith, and Winkler[7] in experimental anuria; the identification of the electrocardiographic alterations as those of potassium poisoning led to the assumption that hyperpotassemia was the cause of death in experimental anuria. This was confirmed by actual determinations of serum potassium. Undoubtedly the T-wave changes after bilateral ureteral ligation described previously by Nicholson and Schechter[10·c] were also due to the rise in serum potassium. Before hyperpotassemia and its reflection in the electrocardiogram were observed in uremia in man, other conditions with a disturbed potassium metabolism were found to show a close relation between serum potassium level and electrocardiogram. This was described, on the one hand, by Thomson[10·d] in a case of Addison's disease with varying serum potassium; on the other hand, by Stewart, Smith, and Milhorat[10·e] in cases of familial periodic paralysis with abnormally low serum potassium during the attacks. Similarly, potassium given by mouth both to individuals without renal impairment and to patients with chronic nephritis[10·f-i] led to transitory electrocardiographic changes characterized by an increase in voltage and decrease in duration of T; the inverted T_1 in cases with left heart strain became less inverted or diphasic and transitory intraventricular block was also observed. The opposite effect on the T wave (leading to lowering or inversion of the T waves) of desoxycorticosterone acetate by lowering of serum potassium was emphasized by Currens and White,[10·j] who considered the electrocardiogram a valuable index in the course of treatment of Addison's disease. The same effect of desoxycorticosterone acetate on the electrocardiogram of normal individuals was observed by Raab.[10·k]

In human uremia, abnormally tall T waves were first described by Wood and White[11·a] in five of thirty-eight patients with uremia many years before their relation to the increase in serum potassium was known. Misske[11·b] found tall peaked T waves which he ascribed to asphyxia in nine of fifty-three cases of uremia and regarded this change in the patient's electrocardiogram as a sign of the approaching death. Finch and Marchand[11·c] recorded electrocardiograms during the terminal stage of two patients with renal insufficiency and fatal potassium poisoning who showed the terminal arrhythmias of potassium intoxication. Keith and co-workers[9] observed the evolution of intraventricular block in three instances of uremia with hyperpotassemia. The intraventricular conduction disturbance appeared less than one week before death in two of their patients. Bywaters[11·d] reported electrocardiographic changes characteristic of potassium poisoning in cases of crush syndrome with hyperpotassemia.

In our own series, five of twenty-five unselected cases of uremia exhibited electrocardiographic evidence of potassium poisoning. This is a rather high

incidence (20 per cent) and probably would have been even higher if more electrocardiograms had been taken in the terminal stage of the disease. It suggests, in contrast to previous reports, that the mode of death in an appreciable number of cases of uremia in man is cardiac standstill or ventricular fibrillation resulting from potassium poisoning of the heart muscle. Six of our patients showed the early sign of potassium poisoning, the characteristic change in T-wave contour without any abnormality of rhythm or disturbance of A-V or intraventricular conduction. The latter changes were present in one case in an electrocardiogram taken less than twenty-four hours before death.

As was mentioned before, the tall potassium T waves of our series, with a single exception, were always associated with a prolonged electrical systole indicative of hypocalcemia. This combination can be considered highly suggestive of uremia. However, prolongation of the electrical systole has been described in Addison's disease,[12] in which condition hyperpotassemia with characteristic T-wave changes can be observed; to our knowledge this is the only other clinical condition which may be responsible for this peculiar combination in the electrocardiogram otherwise diagnostic of uremia.

Disagreement between electrocardiographic interpretation and anatomic evidence represents a real discrepancy in six cases of our series (three cases of pericarditis and three cases of myocardial infarction, Table I). In other cases changes found at necropsy were not reflected in the electrocardiogram because they took place only after the last electrocardiogram had been recorded or because a combination of conditions having opposite effects on the electrocardiogram was present, so that the expected changes may have balanced each other; the latter is particularly true for the effects of chronic left heart strain and hyperpotassemia. It has been emphasized in a previous report correlating electrocardiographic and anatomic findings[13] that old healed myocardial infarcts may no longer be recognizable in the electrocardiogram; this was confirmed in three patients of the present series. It has been shown[14] that diffuse pericarditis does not lead to electrocardiographic changes unless there is a spread of the inflammatory process to the subjacent myocardium. This explains the absence of electrocardiographic evidence of pericarditis in most cases of our series. No instance was encountered showing a combination of pericarditis (concordant elevation of the S-T segments) with potassium changes (tall narrow T waves) which would allow a specific diagnosis of uremic pericarditis; however, a review of the reported cases of pericarditis disclosed one such instance published by Wood and White.[11-a] (Fig. 4)

SUMMARY

1. Twenty-seven fatal cases of uremia are presented and their electrocardiographic and anatomic changes are described.

2. The sole demonstrable characteristic anatomic lesion is pericarditis, which was present in 41 per cent of the series and which frequently extended into the adjacent myocardium.

3. The myocardial changes are those attributed to hypertensive heart disease with additional diffuse fatty degeneration, cloudy swelling of myocardial fibers, and interstitial edema. While the fatty degeneration was probably caused by concomitant anemia, the cloudy swelling and interstitial edema can be attributed to the uremic intoxication but cannot be considered diagnostic of uremia. There is no evidence to support the existence of a specific so-called uremic myocarditis.

4. The factors responsible for the changes in the electrocardiogram of patients with uremia are chronic left heart strain, myocardial changes due to coronary artery disease, diffuse pericarditis, and changes in the electrolyte balance which give rise to hypocalcemia and hyperpotassemia. Because of the opposite effect of some of these factors on the electrocardiogram, the changes tend to obscure or balance each other, as revealed by serial electrocardiograms.

5. Evidence of hyperpotassemia was found in six cases. Tall narrow T waves, which are the early sign of potassium poisoning, were seen in five cases; additional intraventricular and auriculoventricular conduction disturbances, a later sign of potassium poisoning, were present in one case. The terminal stages of potassium poisoning which are characterized by auricular standstill and final ventricular standstill or ventricular fibrillation were not observed, since no tracings were obtained immediately before death.

6. T-wave changes indicative of hyperpotassemia were observed in one case as long as nine weeks before death.

7. The effect of hyperpotassemia on the electrocardiographic pattern of left heart strain is emphasized.

8. The combination of a prolonged electrical systole of the hypocalcemic type with narrow tall T waves indicative of potassium poisoning is the most characteristic electrocardiographic feature of uremia.

9. Potassium poisoning seems to be the immediate cause of death in at least one-fifth of the cases of uremia in man; the electrocardiogram is of value for the diagnosis of hyperpotassemia and thus may give a hint as to the immediate prognosis in patients with uremia.

The authors wish to acknowledge their appreciation of the valuable suggestions of Dr. L. N. Katz and Dr. O. Saphir in this study.

ADDENDUM

After this study was completed, the following articles appeared:

Keith, N. M., Pruitt, R. D., and Baggenstoss, A. H.: Electrocardiographic Changes in Pericarditis Associated With Uremia, AM. HEART J. **31**: 527, 1946. (The authors demonstrated how uremic pericarditis may undergo exacerbations and remissions and may even heal.)

Finch, C. A., Sawyer, C. G., and Flynn, J. M.: Clinical Syndrome of Potassium Intoxication, Am. J. Med. **1**: 337, 1946. (The authors emphasized the clinical importance of the electrocardiographic changes in potassium intoxication in the differential diagnosis between conditions giving rise to paralytic states.)

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SEQUENCE OF VENTRICULAR STIMULATION AND CONTRACTION IN A CASE OF ANOMALOUS ATRIOVENTRICULAR EXCITATION

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ALTHOUGH hypotheses are numerous, many aspects of the phenomenon of anomalous atrioventricular excitation[1] (Wolff-Parkinson-White syndrome,[2] short P-R; bundle branch block syndrome,[3] pre-excitation of the ventricles[4]) are not satisfactorily explained by existing data. The opportunity to study a man who displayed the abnormality intermittently provided answers for two unsettled questions: (1) Is the interval from the beginning of the P wave to the junction of the initial and final ventricular deflections (P-J interval) really or just fortuitously the same during normal and anomalous ventricular excitation? This is equivalent to asking whether conduction by an accessory tract is always accompanied by simultaneous conduction to the ventricles by the normal pathways. (2) What is the mechanical behavior of the ventricles when excitation is anomalous?

OBSERVATIONS ON VENTRICULAR EXCITATION

The patient was a healthy, 27-year-old white man of hypersthenic habitus, a truck driver by occupation, who had no cardiac complaints and whose cardiac examination was negative except for the accidentally discovered electrocardiographic abnormality to be noted.

Initial studies were made on Nov. 5, 1938. The standard leads (I, II, III), the extremity potentials (V_R, V_L, V_F), and the precordial potentials (V_1, V_2, V_3, V_4, V_5, and V_6) were recorded simultaneously with Lead I with the subject recumbent. Two string galvanometers were used, one with a single stage vacuum tube amplifier in circuit. The rate of the auricles and of the ventricles did not fall below 52 per minute, and in this record no abnormal QRS deflections occurred. The standard leads were similar to the normal complexes shown in Fig. 2, a high T wave in Lead I being the only unusual feature. The electrical position of the heart determined from the extremity potentials was semivertical.[5] The precordial potentials were within normal limits.[6] On the same day the standard and special leads were repeated after the intravenous injection of 1.2 mg. of

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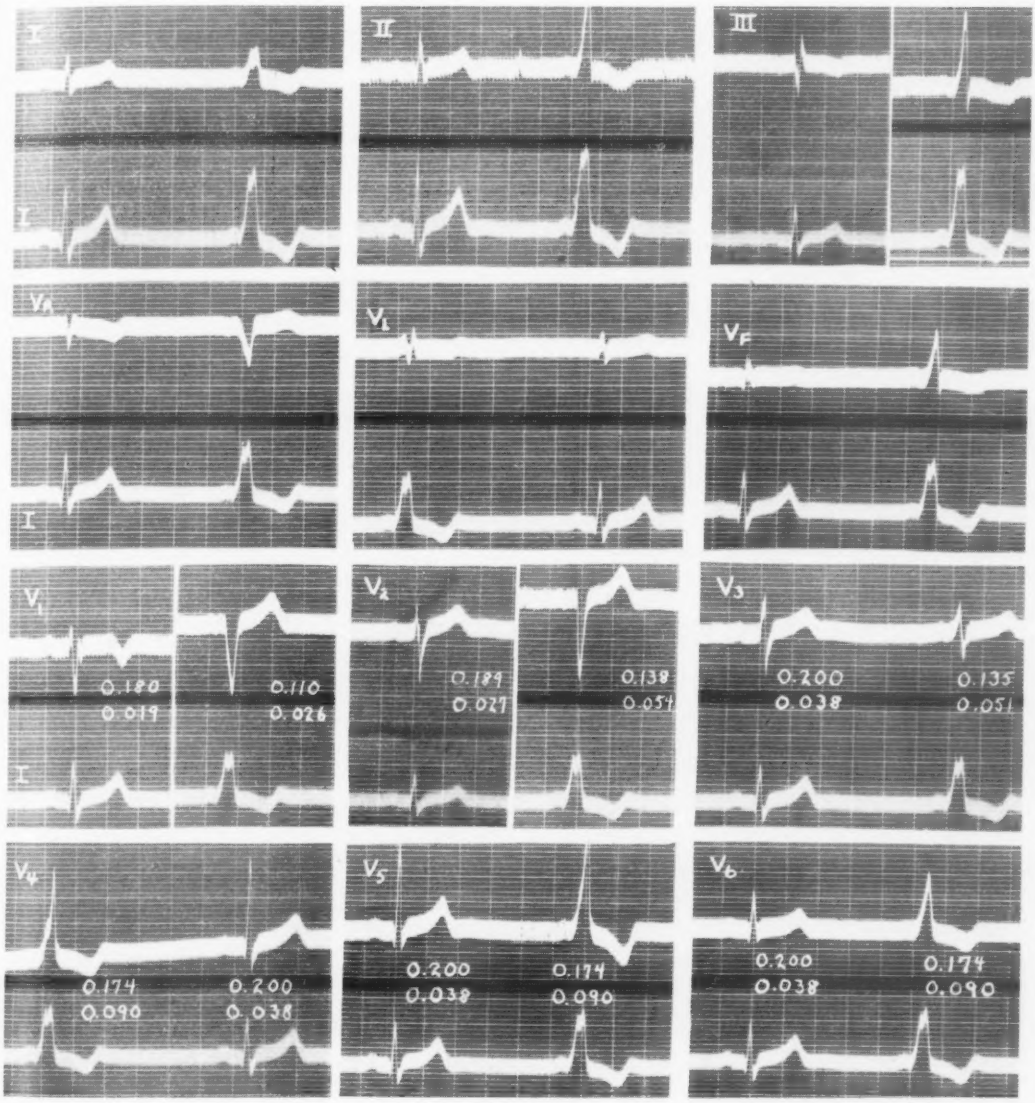

Fig. 1.—Standard and special electrocardiograms recorded on Jan. 21, 1939, with subject recumbent. A normal and abnormal QRS complex has been mounted for each lead. The upper records are: I, standard Lead I; II, standard Lead II; III, standard Lead III; V_R, V_L, V_F are the potentials of the right arm, the left arm, and the left leg, respectively, made with Wilson's method; V_1, V_2, V_3, V_4, V_5, and V_6 are the potentials of the standard precordial points similarly made. The standard leads and extremity leads were made with the string at normal sensitivity (1 mv. = 1 cm.); the precordial leads were made at half normal sensitivity (1 mv. = 0.5 cm.). A vacuum tube was used in the circuit of the string when recording the curves.

The lower string shadow is standard Lead I recorded in the usual way with the string at approximately normal sensitivity but varying somewhat.

Under each precordial lead, both for the normal and abnormal QRS, there are two figures. The upper is the time in seconds from the beginning of P in Lead I to the beginning of the intrinsicoid deflection (peak of R) in the chest lead. The lower figure gives the time between the beginning of QRS in Lead I and the beginning of the intrinsicoid deflection in the chest lead.

atropine sulfate. Except for an increase in heart rate to 95 beats per minute, there were no significant changes.

A similar series of electrocardiograms (Fig. 1) was repeated on Jan. 21, 1939, after the subject had been at rest for a considerable period. When the ventricular rate was in the neighborhood of 50 beats per minute, occasional abnormal ventricular complexes appeared, and at times there were long runs of them alternating with normal ventricular deflections. Rate was not the only determining factor, however, because the QRS was sometimes normal in form even when the rate was below 50 per minute. Wherever possible an adjacent normal and abnormal QRS in the standard and special leads were mounted in Fig. 1 (upper string shadow), each having been recorded simultaneously with standard Lead I (lower string shadow).

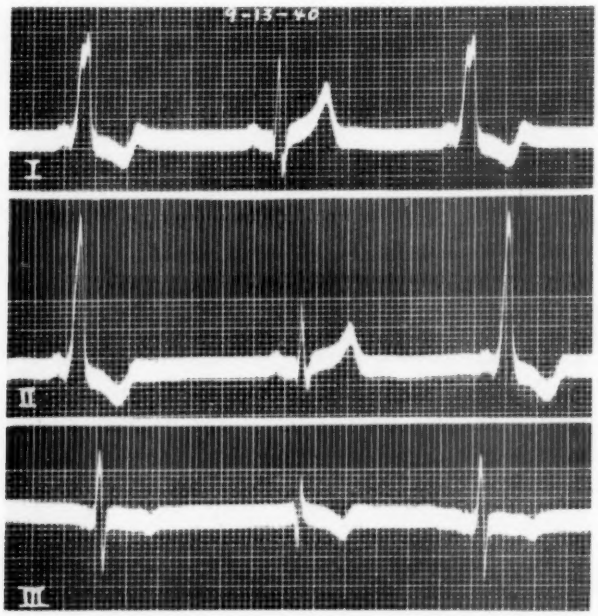

Fig. 2.—Standard leads recorded on Sept. 13, 1940, at a time when normal and abnormal atrioventricular excitation were alternating. In this record the time marker was approximately 4 per cent too fast.

The anomalous complexes, compared with the normal ones in Leads I and II, were characterized by a tall R wave with slurred ascending limb ("anomalous component"),[1] an absence of Q and S waves, and an inversion of T wave which was partial in Lead I. In Lead III, R was larger, the S deeper, and R′ absent; the T wave in this particular record was deeper. There was no difference in the P waves preceding the two types of QRS.[3]

Various intervals (Table I) in the standard leads of this curve were determined by means of a comparator. Leads I and II were measured, but only the results of the former are shown because Lead I lent itself best to precise deter-

TABLE I. INTERVALS IN SECONDS IN STANDARD LEAD I OF RECORDS MADE ON JAN. 21, 1939, AND SEPT. 13, 1940

DATE	P-Q (P-R)		P-R PEAK		P-J		QRS		P-END T		Q-T		K	
	N	A	N	A	N	A	N	A	N	A	N	A	N	A
Jan. 21, 1939	0.154	0.079	0.200	0.174	0.251	0.233	0.097	0.156	0.556	0.530	0.402	0.451	0.367	0.411
Sept. 13, 1940	0.181	0.101	0.226	0.202	0.291	0.272	0.110	0.171	0.623	0.603	0.442	0.502	0.394	0.433

N, normal QRS; A, abnormal QRS resulting from anomalous atrioventricular excitation. Designation of intervals have the usual meaning. P-J was measured from the beginning of the P wave to the junction of QRS with the RS-T segment. K is the systolic index $(Q\text{-}T/\sqrt{R\text{-}R})$.

mination of the beginning of the P and the end of QRS in both normal and abnormal records. The table reveals that during anomalous atrioventricular excitation the QRS interval was 0.059 second longer, the P-R (P-Q) interval was 0.075 second shorter, the P-R peak interval, 0.026 second shorter, and the P-J interval, 0.018 second shorter. The Q-T interval (duration of electrical systole) was much longer in the abnormal QRS and simulated in this regard the findings in bundle branch block.

The potentials of the extremities (V_R, V_L, V_F) revealed that the semivertical, electrical position of the ventricles was unchanged by anomalous excitation. Also, with the latter, the small positive component of Lead V_R and the initial negative component (Q) of Lead V_F disappeared.

In the chest leads the R wave of the anomalous complexes was vestigial in Leads V_1 and V_2, and in this respect the records resembled those which have been designated as "Type B".[1] For each chest lead the time of the intrinsicoid (RS) deflection[7] with respect to the beginning of the P wave in Lead I is indicated by the upper number, and with respect to the beginning of the QRS in Lead I, by the lower number. These are tabulated in Table II.

TABLE II. TIME IN SECONDS OF THE INTRINSICOID (RS) DEFLECTION IN THE PRECORDIAL LEADS WITH REFERENCE TO THE BEGINNING OF P AND THE BEGINNING OF QRS IN LEAD I WITH NORMAL AND ANOMALOUS ATRIOVENTRICULAR EXCITATION

LEAD	AFTER BEGINNING OF P_1				AFTER BEGINNING OF QRS_1			
	(1) NORMAL QRS	(2) ABERRANT QRS	(3) DIFFERENCE	(4) MEAN OF DIFFERENCES	(5) NORMAL QRS	(6) ABERRANT QRS	(7) DIFFERENCE	(8) MEAN OF DIFFERENCES
V_1	0.180	0.110	−0.070	−0.061	0.019	0.026	0.007	0.019
V_2	0.189	0.138	−0.051		0.027	0.054	0.027	
V_3	0.200	0.135	−0.065		0.038	0.051	0.013	
V_4	0.200	0.174	−0.026		0.038	0.090	0.052	
V_5	0.200	0.174	−0.026	−0.026	0.038	0.090	0.052	0.052
V_6	0.200	0.174	−0.026		0.038	0.090	0.052	

a. Difference of means, Columns (1) and (5) = 0.162 (mean P-R interval, normal QRS).
b. Difference of means, Columns (2) and (6) = 0.084 (mean P-R interval, aberrant QRS).
Difference between *a* and *b* = 0.078.

Reference to Table II (Columns 1 to 4) and Fig. 1 reveals that excitation reached all anterior surfaces* of the heart earlier with anomalous excitation. If Leads V_1 and V_2 are regarded as having been from the right ventricle, and Leads V_4, V_5, and V_6 as being from the left ventricle, then the action current with anomalous excitation reached the right side 0.061 second, and the left side 0.026 second earlier than with normal conduction. When the reference point used

*This statement assumes that the peak of the R wave (beginning of the intrinsicoid deflection) marks the time of arrival of excitation at that part of the epicardial surface closest to the exploring electrode. This is probably correct for the greater surface of the left ventricle in man but there is evidence that other variables may be involved in the creation of this deflection over the right ventricle.

was the beginning of QRS in Lead I, then excitation reached the anterior surfaces of the heart later. Referring again to Table II (Columns 5 to 8), with aberrant conduction the intrinsicoid deflection was later on the right side by 0.019 second, and on the left side by 0.052 second.

The "transitional zone"[8] was moved farther to the left with anomalous excitation as usually happens when block of the left bundle branch develops.

These data may be summarized as follows: Although accession began in the ventricles about 0.078 second earlier with anomalous atrioventricular excitation, it did so in a place remote from the normal pathways, for it reached the surface of the right ventricle about 0.017 second later than expected (0.078 – 0.061), and it reached the surface of the left ventricle 0.052 second later than expected (0.078 – 0.026). By measurement from the beginning of ventricular excitation these figures became 0.019 second and 0.052 second, respectively.

On Sept. 13, 1940, the standard leads were repeated (Fig. 2). These differed from previous records in that the normal QRS interval measured 0.110 second compared to 0.097 second on Jan. 21, 1939. At least some of this difference could be accounted for by the difficulty encountered in delineating the end of the S wave, and the remainder by the fact that the telechron timer on the different instrument used was fast by approximately 4 per cent. Although the general contour of both records was the same, there were other differences in intervals as shown in Table II.

In both records the P-J interval was shorter during abnormal excitation by 0.018 and 0.019 second, respectively (Table I), although the R peak of the abnormal QRS was 0.026 second earlier in Leads I, V_4, V_5, and V_6 on the first date (Table I and II), and 0.024 second earlier in Lead I on the second date. This difference was attributable to the longer interval (0.008 second on measurement) from the peak of R to the end of QRS (or J) in the aberrant complexes. This would mean that anomalous atrioventricular depolarization continued in other parts of the ventricles for a longer time after it reached the epicardial surface of the left ventricle than was the case when conduction was through the normal junctional tissues.

OBSERVATIONS ON VENTRICULAR CONTRACTION

Also on Sept. 13, 1940, stethograms were recorded simultaneously with Lead II and with a sphygmogram of the right carotid artery* at a time when anomalous and normal atrioventricular excitation were occurring alternately (Fig. 3). A stethogram at the apex (upper curve) showed only slight differences in the first (S_1) and second (S_2) sounds with the two types of conduction. At the pulmonic area changes were more definite even though the record (lower curve) was somewhat distorted by low amplitude noise. The most interesting differences were the lower amplitude of the first sound and the split second sound with normal conduction. The latter was the reverse of what might be expected.[9-11]

*Records were made with an All-Electric Hindle (Cambridge Instrument Co.). Latency of the sphygmograph was 0.008 second both for the application and discontinuance of a mechanical stimulus.

The right carotid sphygmogram, corresponding to the two types of electrocardiograms, did not differ with regard to amplitude, inclination of the anacrotic limb, or general contour. However, the time of ejection did vary.

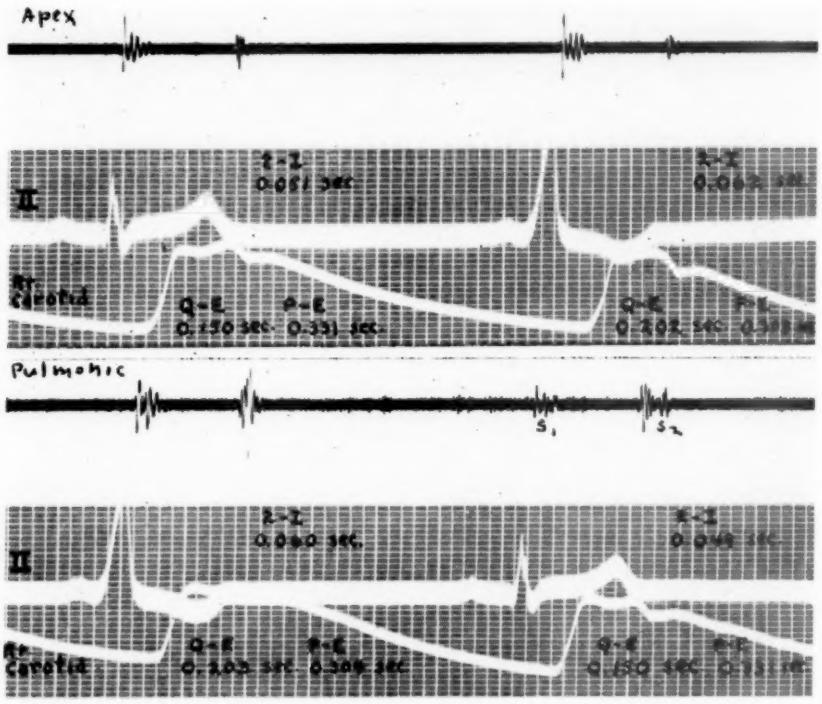

Fig. 3.—Simultaneously recorded stethogram (apex, upper curve; pulmonic area, lower curve), electrocardiogram (Lead II), and right carotid sphygmogram. "Q-E" was measured from the beginning of QRS to the beginning of the rise of the carotid curve; "P-E" was measured from the beginning of the P wave to the beginning of the carotid rise; and "2-I" was measured from the beginning of the second sound to the deepest part of the dicrotic notch (incisura).

The low amplitude, high frequency vibrations on the lower stethogram were caused by outside noise.

In Fig. 3 the "P-E" interval was measured from the beginning of the P wave in Lead II to the beginning of the rise of the carotid pulse curve; the "Q-E" interval was measured from the beginning of QRS also to the beginning of ejection; and the "2-I" interval was measured from the beginning of the second sound to the deepest part of the dicrotic notch (incisura) of the sphygmogram.[9-12] Comparative figures are the most significant especially in view of the electrocardiographic data already given. Relative to the time of discharge of the sinoauricular node (P-E interval), ejection was earlier with aberrant conduction by 0.027 to 0.028 second, but relative to excitation of the ventricular muscle it was 0.052 to 0.053 second later. These figures are almost identical with figures expressing the difference in time of arrival of excitation at the epicardial surface of the left ventricle with the two types of excitation (Table II). This would indicate that anomalous atrioventricular excitation affected both electrical and

mechanical events, at least in the left ventricle, in the same direction and to the same extent. Latency of the sphygmograph and probably of the velocity of the pulse wave from the heart to the carotid artery were constant for both types of conduction and hence play no part in the calculations as made.

Absolute values of the Q-E interval and the 2-I interval are to be compared with similar values obtained in normal subjects and in a few patients with left or right bundle branch block (Table III). Identical equipment was used in making these records. In the aberrant complex (Fig. 3) the Q-E interval of approximately 0.203 second and the 2-I interval of approximately 0.062 second simulate the findings with block of the left bundle branch (Table III).

TABLE III. MINIMUM, MAXIMUM, AND MEAN VALUES IN SECONDS OF THE Q-E INTERVAL (BEGINNING OF QRS TO BEGINNING OF CAROTID EJECTION) AND THE 2-I INTERVAL (BEGINNING OF SECOND SOUND TO DEEPEST POINT OF DICROTIC NOTCH), USING THE RIGHT CAROTID PULSE AND STANDARD LEAD II IN NORMAL SUBJECTS AND IN PATIENTS WITH LEFT AND RIGHT BUNDLE BRANCH BLOCK*

		NORMAL (8 SUBJECTS) QRS INT.: 0.064 TO 0.080	LEFT BUNDLE BRANCH BLOCK (3 PATIENTS) QRS INT.: 0.125 TO 0.168	RIGHT BUNDLE BRANCH BLOCK (5 PATIENTS) QRS INT.: 0.126 TO 0.145
Q-E	Minimum	0.131	0.195	0.120
	Maximum	0.148	0.233	0.180
	Mean	0.1392	0.2127	0.1508
2-I	Minimum	0.047	0.063	0.022
	Maximum	0.060	0.084	0.060
	Mean	0.0521	0.0770	0.0400

*The same apparatus was used as in making the records shown in Fig. 3.

By way of summary, the stethographic and sphygmographic data indicate that with anomalous atrioventricular excitation in this subject there was asynchronous contraction of the ventricles. Although in point of absolute time, measured from the initial discharge of the sinoauricular node, the left ventricle ejected blood earlier than normal, with respect to beginning depolarization in the ventricle it ejected blood later than normal and in this regard simulated conditions found when there is block of the left bundle branch.

DISCUSSION

The data presented favor the conclusion that in this subject anomalous atrioventricular excitation was not accompanied by conduction through the bundle of His as in previously reported cases.[1] Specifically two groups of facts lead to this conclusion: (1) All electrical events were earlier in both ventricles with pre-excitation than with normal conduction. These events include the beginning and end of QRS and the peak of R both in the standard and the precordial leads. (2) When the P-R interval was short the left ventricle

was depolarized (and repolarized) completely in a right to left direction as with block of the left bundle branch. The evidence for this was the prolongation of electrical systole (Q-T interval), the considerable delay from the time excitation entered the ventricles until it reached the epicardial surface of the left ventricle, and the stethographic and sphygmographic evidence of delayed ejection of the left ventricle. That the anomalous complexes differed in contour from the usual pattern seen with left bundle branch block does not seem to be a valid objection. In fact, a difference would be expected by virtue of the different manner of excitation of the contralateral ventricle in this syndrome compared to bundle branch block.

The mechanism by which conduction from auricles to ventricles was accomplished, exclusive of the usual pathways, seemed to depend upon the relative prematurity of conduction by the anomalous pathway, if such exists. Presumably, excitation entered the right ventricle so early that it had already spread in an aberrant fashion to the left ventricle, and that chamber was refractory at a time when an impulse reached it through the common bundle and left bundle branch.

Whether this always occurs in the type of electrocardiogram under discussion when the P-R interval is shortened beyond a certain "critical value" is not known. Existing data suggest that it should occur when the P-R interval with the anomalous complex is shortened by approximately 0.06 second or more.

This figure was arrived at in two ways, both concerned with determining how long it takes excitation to spread from one side of the human heart to the other as when a bundle branch is blocked. First, an approximation was made by comparing the QRS interval in the electrocardiograms of ten patients before and after the development of complete (QRS interval of 0.12 second or more) bundle branch block, either left or right. Admittedly, many variables come into

TABLE IV. TIME (SECONDS) OF AURICULOVENTRICULAR AND INTRAVENTRICULAR CONDUCTION IN REPORTED CASES OF INTERMITTENT ANOMALOUS ATRIOVENTRICULAR EXCITATION

AUTHORS	CASE	NORMAL CONDUCTION			ABNORMAL CONDUCTION			DIFFERENCE IN P-R INTERVALS
		P-R	QRS	SUM	P-R	QRS	SUM	
Wolf, Parkinson, White 1930[2]	1	—	—	—	—	—	—	0.06
	2	—	—	—	—	—	—	0.05
	3	—	—	—	—	—	—	0.10
	4	—	—	—	—	—	—	0.06
	8	—	—	—	—	—	—	0.06
Moia and Inchauspe, 1938[14]	—	0.16	0.06	0.22	0.09	0.12	0.21	0.07
Hunter, Papp, Parkinson, 1940[3]	3	0.14	0.08	0.22	0.12	0.11	0.23	0.02
Wolferth and Wood, 1941[18]	A. B.	0.17	0.08	0.25	0.13	0.11	0.24	0.04
Missal, Wood, Leo, 1946[19]	—	0.16	0.08	0.24	0.11	0.12	0.23	0.05
Rosenbaum, Hecht, Wilson, Johnston, 1945[1]	5	0.160	0.078	0.238	0.122	0.122	0.244	0.038
Kossmann and Goldberg, 1946	—	0.154	0.097	0.251	0.079	0.156	0.235	0.075
		0.181	0.110	0.291	0.101	0.171	0.272	0.080

such a calculation, particularly relative hypertrophy of the interventricular septum and the chambers. Nevertheless, in the ten cases investigated the minimum lengthening of QRS by block of a bundle branch was 0.04 second, the maximum was 0.09 second, and the mean was 0.060 second. Second, the records published by Barker, Macleod, Alexander, and Wilson[13] obtained by stimulating the exposed human heart were measured grossly with a hand lens. The supraventricular QRS was 0.08 second in length; the QRS interval of premature systoles induced in either ventricle was 0.13 to 0.14 second.

To test the concept further an attempt was made to learn what the usual shortening of P-R interval was in published cases of intermittent anomalous atrioventricular excitation. Unfortunately, most authors have not provided these data. Table IV contains published measurements found and also gross measurements made by us on electrocardiograms reproduced in several published articles, using the lead in which the normal P-R interval was longest. It simply shows, with three exceptions including the present case, that excitation of the ventricles in the syndrome under consideration is usually premature by less than 0.06 second. In one of the three exceptions[14] asynchronous contraction of the ventricles was demonstrated. In the case reported here anomalous ventricular excitation was premature by an average of 0.078 second in two records made with an intervening interval of twenty months.

CONCLUSIONS

The findings presented favor the concept of an accessory pathway[15,16] in anomalous atrioventricular excitation, and also help to explain some controversial matters. The variable reports[14,17] on asynchronous contraction of the ventricles can be reconciled. Asynchronism will depend on the degree of prematurity of ventricular excitation. Further, the nature of the asynchronism will depend on whether the accessory pathway connects the auricles with the right ventricle or with the left ventricle.

Previous explanations[17] for the occurrence of transitional complexes, such as published by Hunter, Papp, and Parkinson (Case 3), on the basis of a variable rate of conduction in the junctional tissues and the relative amounts of cardiac muscle stimulated through each pathway are favored by the findings in the present case. Possibly the failure to get much change in QRS with induction of A-V nodal rhythm in certain cases may also be based on very early excitation of the ventricles by the anomalous pathway whenever it functions. Under such circumstances shortening of the normal A-V conduction time would have only a partial effect. The findings also explain why in some cases with anomalous conduction and auricular premature systoles, the QRS complexes of the latter vary a little from those of the usual supraventricular beats.[18]

SUMMARY

1. In a case of intermittent anomalous atrioventricular excitation it was found that the interval from the beginning of the P to the end of the QRS was shorter with the anomalous than with the normal beats.

2. These and other data are interpreted to mean that depolarization of the ventricles was mediated entirely through an accessory pathway in the right

ventricle, and that there was no conduction through the normal A-V conduction system when the QRS complexes were anomalous.

3. Considerable delay in ejection of the left ventricle compared to the right occurred when the P-R interval was short.

4. It is suggested that in different individuals with the syndrome, and sometimes in the same individual, variations in the relative amounts of ventricular muscle excited by impulses reaching it through the normal pathway on the one hand and through an accessory bundle or bundles on the other, readily explains many observations which have heretofore been regarded as conflicting.

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THE VOLUME ELASTICITY OF THE AORTA IN THE INTACT DOG

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THE large elastic arteries act not only as conduits for the passage of blood, but serve also during systole as a storage point for part of the blood ejected by the heart. Through this mechanism these vessels accumulate energy during systole which they release during diastole. They form, therefore, a compression chamber or "Windkessel" which helps assure a constant flow of blood into the peripheral blood vessels. A large part of the heart's energy is used in filling this compression chamber.[1] The enlargement of the compression chamber is most rapid early in systole when the pressure within it is low,[2] but the compression chamber reaches its maximum size toward the end of systole.[3] Most of the decrease in its size occurs early in diastole.[4] The fluctuations in size of the compression chamber are determined by its distensibility which declines as the internal pressure rises. The elasticity of the various components of the compression chamber is unequal. Thus, the elasticity of the aorta diminishes toward the periphery.[5] Age, also, causes a decline in its elasticity.[6] The size of the compression chamber increases with the size of the animal in different species.[7]

It is thus apparent that the characteristics of the compression chamber play as important a role in cardiovascular dynamics as do those of the heart and peripheral resistance. Our information on the elastic properties of the large arteries has depended, to a large extent, upon studies of the isolated aorta and large vessels[8,9] and upon indirect evidence involving measurements of pulse wave velocities and pressure pulses.[10] There appear to be no direct observations of the distensibility or elasticity of the compression chamber or any of its component parts in the living animal, aside from the studies of Wiggers and Wegria,[11] who used an aortograph to determine the changes in diameter of one portion of the aorta simultaneously with the pressure changes in the root of the aorta. This impelled us to seek more information on this important physiologic subject. The newer techniques which have been developed in the study of angiography suggested that data on the size of the aorta might be obtained in intact animals and that from this data information concerning the properties of the compression chamber might be derived. In the present report we wish to describe a technique

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developed for the purpose of measuring the distensibility curve of the aorta in the living dog with chest closed. The findings so obtained are compared with the distensibility of the aorta found immediately after the death of the animal.

METHODS

Seven dogs weighing from 15 to 25 kilograms and anesthetized with nembutal (25 mg. per kilogram) were utilized in these studies. The portion of the descending thoracic aorta to be used for measurement was marked off with two small (1 cm. by ½ cm. by ½ mm.) metal grids which were sewed onto the adventitia at the level of the fourth and tenth intercostal spaces. For this purpose the aorta was exposed by two small openings on the left side of the chest, the dog meanwhile being maintained under artificial respiration. After placement of the grids the chest was closed, the pneumothorax relieved, and the animal permitted to breathe spontaneously. The animal was then heparinized by the intravenous administration of 3 to 4 c.c. of heparin,* after which two radiopaque catheters, 3.8 mm. in diameter, were introduced under fluoroscopic control. One was passed via the left carotid artery into the upper part of the ascending aorta. The other was passed via the left femoral artery into the descending thoracic aorta until its tip lay equidistant between the two grids; this catheter was then connected to a Hamilton manometer[12] to record the pressure pulse in the aortic segment to be studied. The upper catheter was used to inject Diodrast† for the x-ray visualization of the aorta. The animal, lying on its left side, was placed beneath the x-ray tube. Diodrast (20 c.c. of 70 per cent solution) was injected rapidly; immediately upon completion of the injection an x-ray picture (lateral view) was taken.‡ The time of the x-ray exposure was recorded on the blood pressure record by means of a signal magnet. This was repeated a number of times without moving the animal or the x-ray tube. The x-ray photographs were taken at 25-inch tube distance, using 100 milliamperes, 75 kilowatts, and 0.1 second exposure. The dogs were bled from time to time in order to obtain a wide range of arterial pressures for each animal during the course of the experiment. This procedure was repeated until the animal succumbed.

Immediately after death the aorta was removed and the intercostal arteries tied close to the aorta; care was exercised to prevent constriction of the aortic wall by this maneuver. The upper end of the aorta then was tied off at the upper end of the proximal grid, and the lower end, at the lower end of the distal grid, was tied over a cannula attached to a syringe and a manometer. All the air in the system and aorta was withdrawn and replaced with physiologic saline solution. Measured increments of saline were injected into this isolated aorta and the resulting pressures measured on the manometer. After the desired maximal pressure was reached, enough fluid was removed to cause a return to atmospheric pressure. The measurements were repeated three times in succession. This procedure gave the pressure-volume (P/V) curve of the isolated aorta directly.

*We are indebted to Roche Organon, Inc., Nutley, N. J., for liberal supplies of Liquemin.
†We are indebted to Winthrop Chemical Co., Inc., New York, N. Y., for liberal supplies of Diodrast.
‡We are indebted to Dr. R. Arens, of the X-ray Department, for making available the facilities of his department.

The volume of the identical portion of the descending aorta in the living animal was calculated from the area and length of the aorta between the outer edges of the two grids in the lateral roentgenograms. The area was measured by planimetry after the margins of the aortic shadow were outlined in ink on the film. The planimeter reading was obtained at least five times for each film and the average recorded. The length of the aortic segment was measured with a flexible rule laid on the film halfway between the margins of the aortic shadow and curved to follow the curvature of the shadow. The average radius was computed from these two measurements. It was considered more accurate to obtain the average radius by computation of the aortic segment's area divided by twice the length than by direct measurement in several locations.

The volume of the aorta then was calculated as follows:

$$V = \pi \cdot r^2 \cdot K^2 \cdot lK = \pi \cdot r^2 \cdot K^3 \cdot l$$

where r and l are radius and length of the segment and K is a factor introduced to correct for the distortion of the x-ray tube. K was determined by dividing the known actual diameter of the lower catheter by the diameter of its x-ray shadow in the film.

The errors involved in this method of computing the volume of the aorta were checked in two isolated aortas filled with known increasing amounts of diodrast. Roentgenograms were taken of the aorta and of a catheter placed next to it, and the volume of the isolated aortas was calculated in the same manner as in the in vivo experiments. The results obtained were compared with the amount of fluid actually injected. The data given in Table I indicate a good agreement. An error which the control calculation does not reveal is due to the possibility that at low pressures the aorta may not be perfectly cylindrical so that the conversion of area to volume might be inaccurate. Furthermore, the

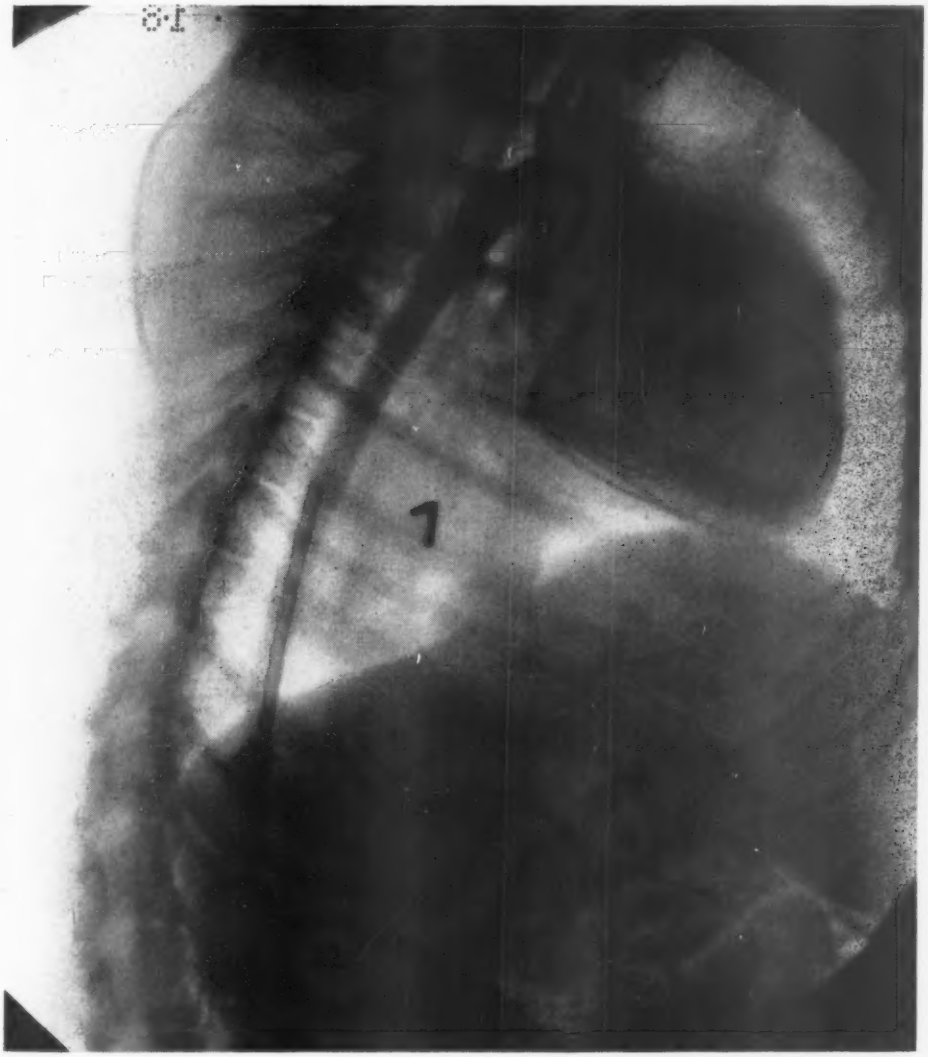
TABLE I. CONTROL OF THE CALCULATION OF AORTIC VOLUME IN VIVO

ACTUAL VOLUME INJECTED (C.C.)	VOLUME CALCULATED FROM X-RAY (C.C.)
A. Isolated Aorta of Dog 10	
4.0	4.4
5.0	5.3
6.0	6.2
7.0	7.1
8.0	8.4
B. Isolated Aorta of Dog 22	
2.6	2.7
3.6	3.5
4.6	4.6
5.6	5.5

A.

Fig. 1.—Roentgenograms of the diodrast-filled aorta in situ in the living dog (lateral view). *A*, Taken when the mean pressure in the thoracic descending aorta was 97 mm. Hg. *B*, Taken when the mean pressure in the thoracic descending aorta was 51 mm. Hg. *C*, Taken after the death of the animal, the aortic pressure being 0 mm. Hg. In each, the two catheters are seen in the aorta, the upper one passing down into the ascending aorta and showing diodrast escaping into the sinuses of Valsalva, the lower one passing up into the descending thoracic aorta with its opening halfway between the two grids (crosshatching) fastened to the aorta. The shadow of the heart and liver can be seen with diodrast filling the coronary and hepatic arteries. The filling of the aorta and these two systems of arteries are seen best in *C*, since absence of respiratory and cardiac motion and of blood circulation, respectively, makes for less fuzziness and less diodrast dilution. In *C*, the intercostal vessels are clearly visible. The visualization of the coronaries in life has been reported previously.[13] The increase in the diameter of the aorta in *B* compared to *C* and in *A* compared to *B* is clearly seen. Comparisons of *A*, *B*, and *C* also show that increase in arterial pressure causes (1) a progressively greater distensibility of the aorta from the diaphragm to the semilunar valves; (2) an increase in the distance between the ascending and descending parts of the arch of the aorta; and (3) an elevation of the arch. The method of calculating the area of the thoracic aorta between the grids and converting it into volume is given in the text. Other details also are discussed in the text.

grids marking the limits of the aortic segment changed their angle as the size of the aorta altered (Fig. 1) and introduced an error in determining length. Another possible error inherent in our method lies in the determination of pressure. This was measured as the mean pressure by planimetry of the pressure-

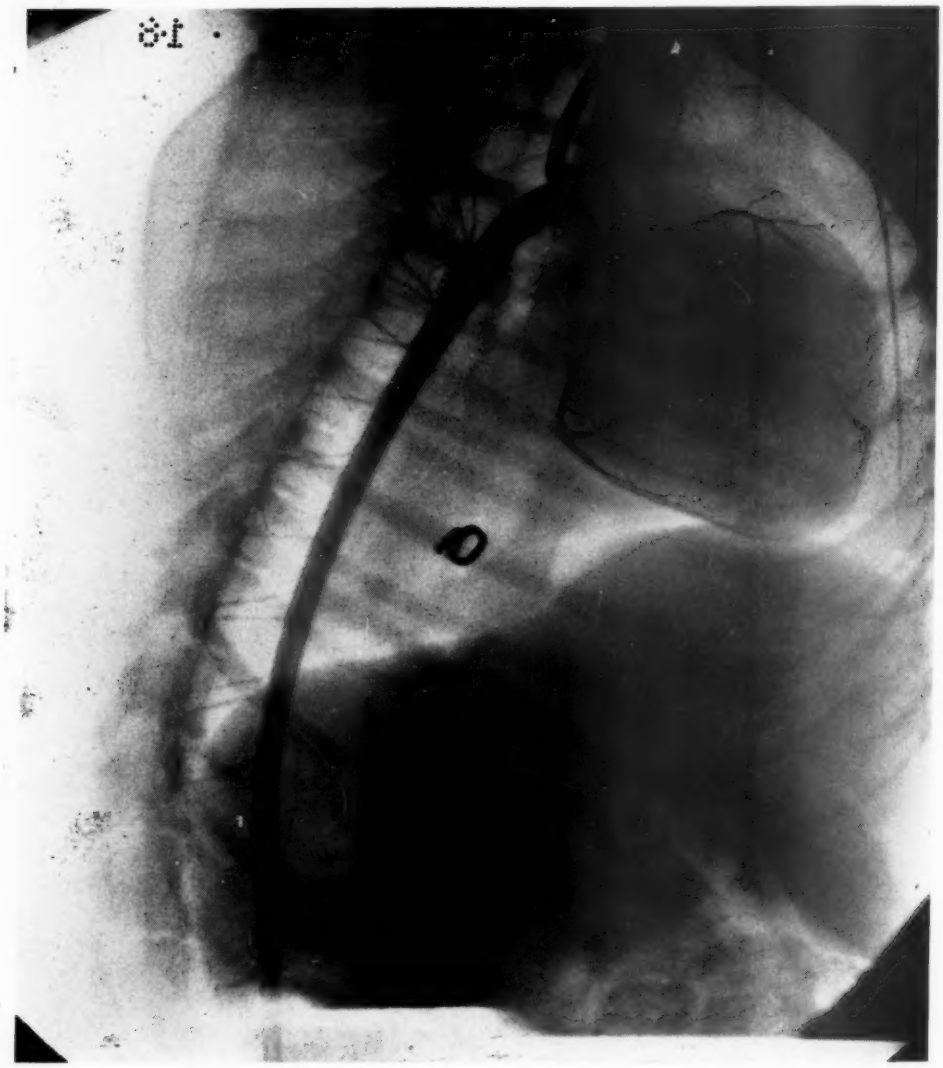


B.

Fig. 1 (Cont'd).—*For complete legend, see opposite page.*

pulse curve, whereas the volume calculated is more likely to be the systolic volume. It has been shown that the pressure pulses in various parts of the aorta are not identical and to some extent this is true also of the segment of aorta under consideration. By taking the measurements in the middle of the

aortic segment, however, a close approximation of the average pressure in the segment should have been obtained. Finally, the catheter measured end pressure rather than the slightly lower lateral pressure actually impinging upon the aortic wall.



C.

Fig. 1 (Cont'd).—*For complete legend, see page 322.*

The scatter of individual points from the pressure-volume curve obtained in vivo is attributable to several random errors. Among these are the following: (1) The movements of the grids mentioned cause the length measurement of different roentgenograms to vary from its true value; (2) the inaccuracy of outlining

the margins of the aortic shadow, together with the inaccuracy in the length measurements, causes the area outlined on the roentgenogram to vary from its true size; (3) the time of x-ray exposure, 0.1 second, is a variable part of the heart cycle, so that the mean pressure calculation based on the complete heart cycle will vary from the mean pressure actually existing during the x-ray exposure; (4) variations in the processing of the x-ray films may bring out varying degrees of diffusion which cause variations from their true dimensions in the shadow of the aorta and the catheter within it. From these considerations it is apparent that the measurements made in vivo are to be considered as approximations of the actual pressure-volume relationship. There is need for a more accurate approach, but the present method appeared to be sufficiently accurate to reveal trends.

In order to make the figures comparable, the volumes were converted to volumes for a standard length of aorta (10 cm.) by multiplying by ten divided by the actual length. The volume so obtained was plotted as percentage of the volume at 55 mm. Hg. These P/V curves were used as an index of the distensibility of the various aortas.

RESULTS

The P/V Curve of the Descending Thoracic Aorta in the Living Animal.—When the volumes of the aortas were corrected for standard length and plotted as percentages of the volume at 55 mm. Hg, the pressure-volume curves of the seven dogs fell into two groups of different slope, as shown in Fig. 2. In five

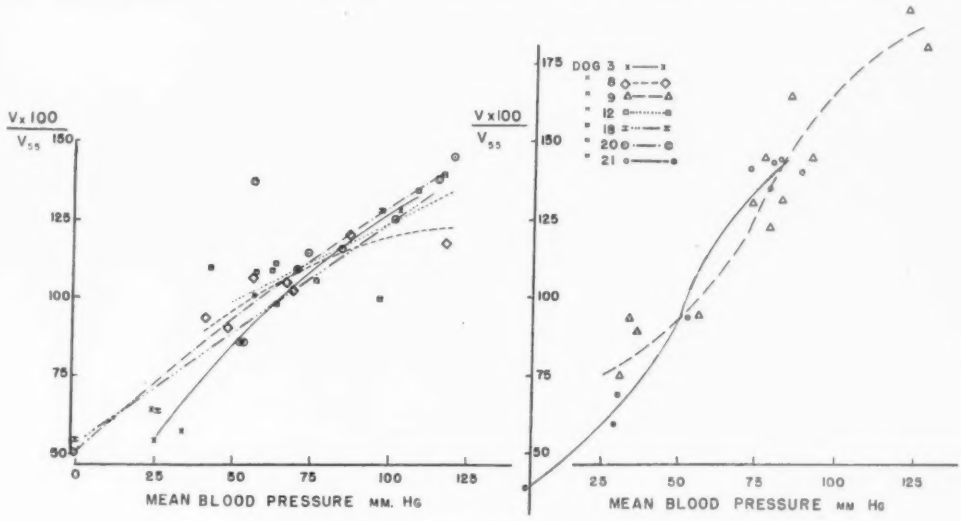


Fig. 2.—P/V curves as calculated for the descending thoracic aorta in seven living dogs. Discussed in text.

dogs the slopes coincided reasonably well, as shown on the left; in the other two dogs the slopes were much steeper, as shown on the right. Furthermore, the curves showed differences in contour. It is thus apparent that the inherent

distensibility of the aorta in vivo varies from animal to animal even after the differences due to different length and diameter are eliminated. These differences undoubtedly represent variations in the elasticity of the various components of the aortic wall. Age differences in the animals are probably not the sole influence.

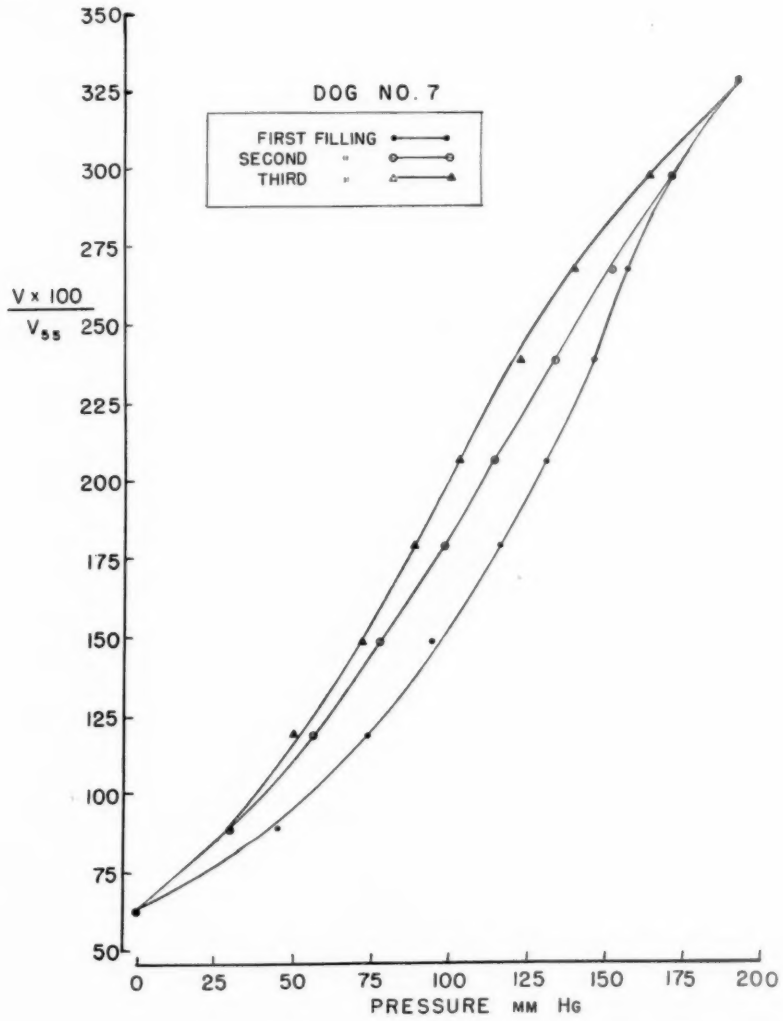


Fig. 3.—Dog 7. P/V curve of the isolated descending thoracic aorta in one dog showing the alteration in its contour in three successive fillings. Discussed in text.

The P/V Curve of the Isolated Aorta.—In confirmation of the finding of Krafka,[8] we have found that repeated distention of the isolated aorta alters the shape of the P/V curve. A typical experiment is illustrated in Fig. 3. Volumes are again expressed as values at 10 cm. length and as percentage of the volume at 55 mm. Hg of the initial stretch. It will be seen that for the pressure

range between 0 and 200 mm. Hg, the P/V curve starts and ends at the same points for the three stretchings. In the second distention, however, intermediate points show a greater volume for a given pressure, and in the third a further increase of volume at these pressures is seen.

It was found that four of the five isolated aortas were remarkably alike (Fig. 4) when the P/V curves of the first distention were compared. The fifth aorta coincided with the others at lower pressures but showed less distensibility at higher pressures.

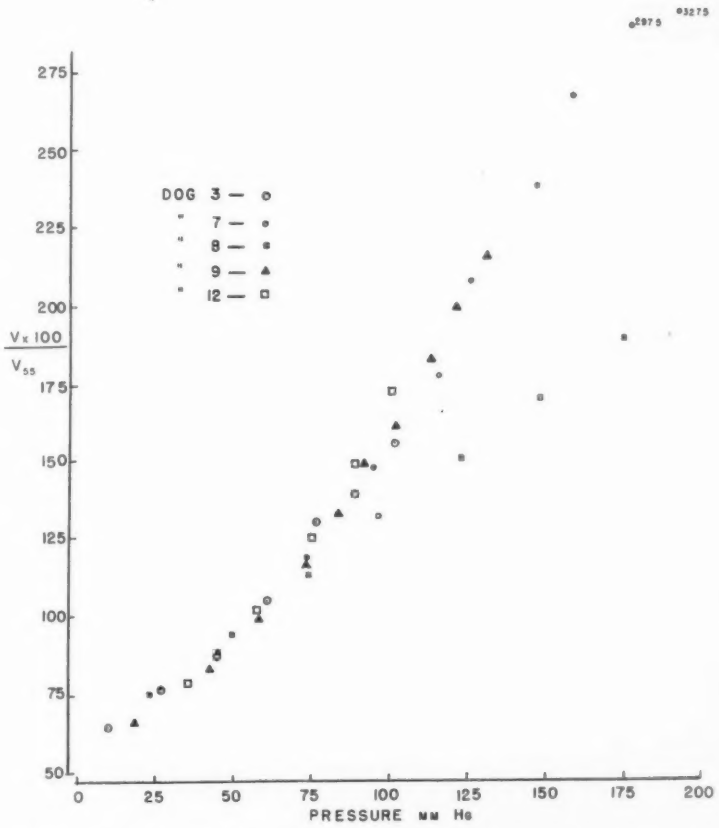


Fig. 4.—Initial filling P/V curves of the isolated descending thoracic aorta in five dogs. Discussed in text.

In four animals, the distensibility curve of the isolated aorta could be compared with that obtained in the living animal. This comparison is shown in Figs. 5, 6, 7, and 8. In the isolated aorta the values obtained for the first distention were used. It will be seen that the P/V curves obtained in living animals and in isolated aortas differ from each other in slope in all cases, some more than the others. In all, there is a tendency for the aorta in vivo to be less distensible at higher pressures than the isolated aorta. In Dog 9, this difference is slight, in Dog 12 it is marked, and in the other two dogs it is intermediate.

The comparison between the distensibility curves in living and isolated aortas suggest that the distensibility of the aorta in vivo cannot be accurately determined by measuring the distensibility of the isolated aorta but must be determined in the intact animal.

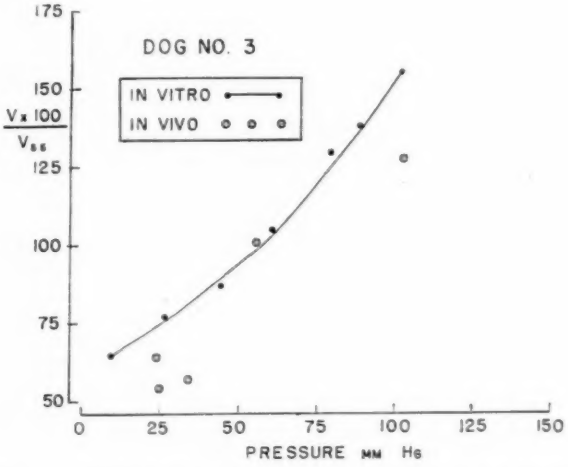


Fig. 5.—Dog 3. P/V curve obtained from in vitro initial distention of the descending thoracic aorta compared with the P/V values obtained in vivo. Discussed in text.

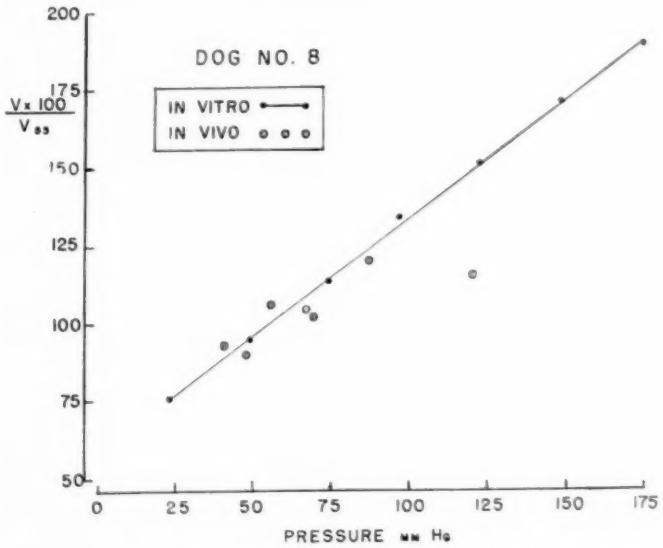


Fig. 6.—Dog 8. P/V curve obtained from in vitro initial distention of the descending thoracic aorta compared with the P/V values obtained in vivo. Discussed in text.

In explaining the difference between the in vivo and in vitro distensibility curve in the intact and isolated aorta, the difference in systolic uptake of the various parts of the aorta may play the significant role. Since the volume of the

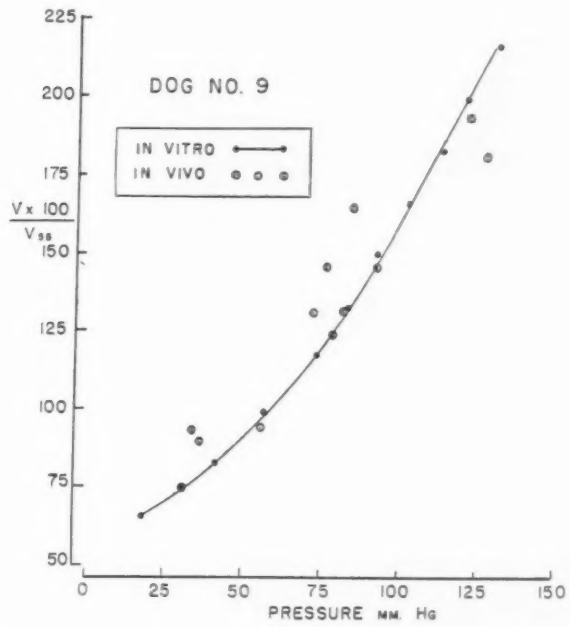


Fig. 7.—Dog. 9. P/V curve obtained from in vitro initial distention of the descending thoracic aorta compared with the P/V values obtained in vivo. Discussed in text.

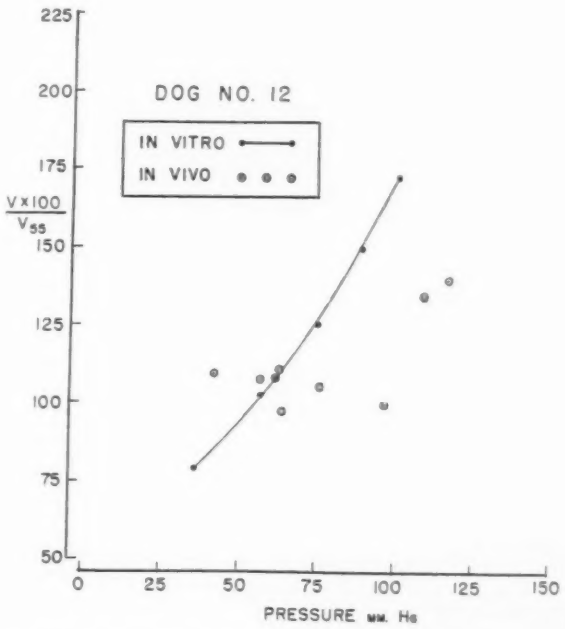


Fig. 8.—Dog. 12. P/V curve obtained from in vitro initial distention of the descending thoracic aorta compared with the P/V curves obtained in vivo. Discussed in text.

aorta so obtained in vivo is probably the systolic volume, differences in the distensibility of the parts of the compression chamber will mutually influence the systolic uptake of each part. Examination of Fig. 1 will show that the ascending aorta and arch are more distensible than is the descending thoracic aorta. This is associated not only with a much greater increase in diameter of the upper part of the aorta at higher pressures, but also with a greater separation of the anterior and posterior segments of the arch and a more cephalad placement of the arch.

SUMMARY

1. A new method for determining the volume of the descending thoracic aorta in the intact dog is described. This method makes use of diodrast-angiography and makes possible the direct determination of the distensibility of the aorta in the living animal.

2. Data depicting the pressure-volume relationship of this segment of the aorta in the intact dog were assembled from seven dogs. Similar data were obtained for the same segment of the aorta immediately after death in five dogs. The volumes were converted to standard length and diameter in order to compare the data of one animal with those of another and also to compare the data obtained in the living animals with those obtained in the isolated aorta.

3. The errors of the method are discussed.

4. It was found that in the living animal considerable variation existed from dog to dog in the contour of the pressure-volume (P/V) curve. The pressure-volume curve fell into two general slopes, however; the aortas of five dogs fell along the less distensible curve and the aortas of two dogs fell along the more distensible curve.

5. Consistent deviations were found in the pressure-volume curves in the isolated aortas obtained in three successive fillings. While starting and ending at the same point (at pressures of 0 and 200 mm. Hg), in each successive filling the aorta was more distensible at intermediary pressures.

6. The pressure-volume relationship of the first distention in four of five isolated aortas was remarkably uniform. That of the fifth aorta coincided with the P/V curve of the other four at lower pressures but deviated from it at the higher pressures.

7. The discrepancy between the pressure-volume relationship found in the living animal as compared with the more consistent P/V curve in the isolated aortas indicates that the distensibility of the aorta in vivo cannot be depicted accurately by measurements on the isolated vessel. This was confirmed by actual comparison of the P/V relationship of the aorta in vivo and the isolated aorta in four animals.

8. The differences between the distensibility curves of the intact and isolated aorta are attributed to the differences in systolic uptake of the various parts of the compression chamber. Such variation in distensibility of the parts of the aorta was readily discernible in the roentgenograms (lateral view) taken of the entire thoracic aorta. At increasing pressures the upper part of the aorta and the arch increased in size to a greater extent than did the lower descending thoracic aorta with which this study concerned itself.

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THE DIAGNOSIS AND TREATMENT OF THROMBOANGIITIS OBLITERANS IN THE VASCULAR CENTERS OF ARMY GENERAL HOSPITALS

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THE clinical and other features of thromboangiitis obliterans, as encountered in the Armed Forces, did not differ from those observed in civilian practice except that the condition was seen generally in the early stages and very few old, long-standing cases were encountered. The data which form the basis of this report were assembled from the three vascular centers (Fig. 1).*

CLINICAL FEATURES

Incidence.—Thromboangiitis obliterans constituted a small but appreciable proportion of the cases admitted to the vascular centers. Of a group of 3,778 vascular cases, the diagnosis of thromboangiitis obliterans was made in 274 patients, or 7.2 per cent of the total.

Duration of Symptoms.—In fifty-three cases reported from Ashford General Hospital, the average duration of symptoms was 21.9 months, the shortest duration being one month and the longest thirteen years. Occasionally, the diagnosis of thromboangiitis obliterans was made in one of the vascular centers only after the patient had been under examination and treatment in many installations in which a variety of diagnoses had been made. In such instances highly specialized diagnostic procedures, which included determinations of skin temperature, oscillometry, and even arteriography or biopsy of the affected vessel, were required before the correct diagnosis was made.

Sex.—Thromboangiitis obliterans almost exclusively affects men, although occasional cases have been reported in which evidence of its presence has been found in women. There have been no reports from any of the vascular centers of its occurrence in women.

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*Major Jacob H. Kahn supplied the data from the Vascular Section, Ashford General Hospital. The material from the Vascular Surgical Section, Mayo General Hospital, was assembled by Lieutenant Colonel Harris B. Shumacker and that from the Vascular Medical Section, Mayo General Hospital, by Major David I. Abramson. Major John V. Waller compiled the figures from the Vascular Medical Section, DeWitt General Hospital. To each of these officers I wish to express appreciation for their helpful cooperation.

Race.—Although originally thromboangiitis obliterans was believed to occur chiefly in the Jewish race, subsequent investigations have shown that its occurrence is far more widespread. It has been encountered in individuals of every nationality. In the present series, of 150 patients in whom the race was recorded, thirty-two (20 per cent) were Jews. Although the disease supposedly is rare in the Negro, seven cases were reported from the vascular centers in which the diagnosis was confirmed by biopsy or by the typical clinical picture which the Negro patient presented.

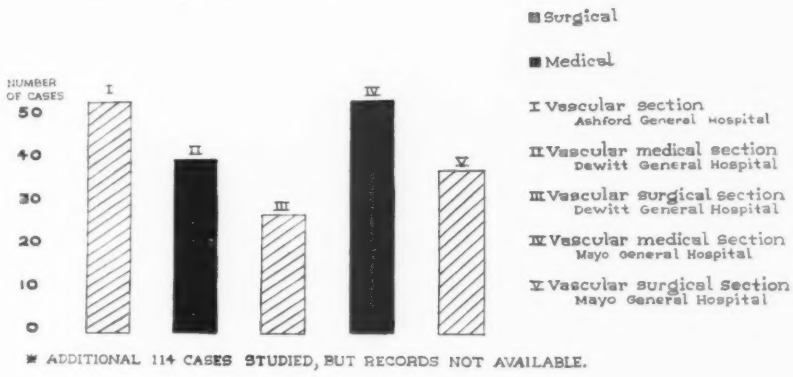

Fig. 1.—Sources of material on thromboangiitis obliterans.

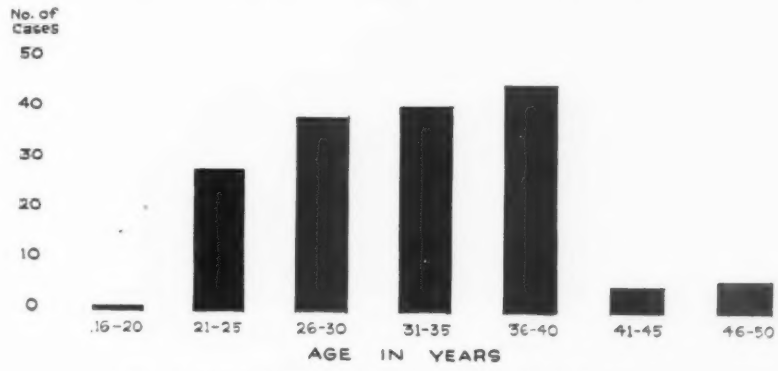

Fig. 2.—Age of patients with thromboangiitis obliterans.

Age.—In Fig. 2 is shown the age distribution in 152 of the patients with thromboangiitis obliterans. Ninety-two per cent of the cases fell within the age period 26 to 40 years. The relatively low reported incidence in patients under 25 years of age may be explained on the basis that the disease, although present, had not advanced sufficiently to produce symptoms.

Symptoms.—The symptoms presented by the patients at the time of admission are shown in Fig. 3. As can be seen, intermittent claudication, which Homans[1] has termed "the one characteristic early evidence of the disorder," was the complaint most frequently noted (67 per cent). This intermittent limp-

ing was most often associated with pain in the foot and leg. Sixty per cent of the patients complained of some form of pain in the extremities. Temperature difference, either subjective or objective, was observed in 45 per cent of the patients. Twenty per cent complained of some disturbance of sensation, chiefly numbness, especially after walking. Ulceration was present in 20 per cent, although gangrene was observed in only 4.4 per cent of the series. Vasomotor disturbances characteristic of Raynaud's phenomenon were observed in nine patients. Migratory phlebitis was found in slightly less than one-third of the patients. This incidence is approximately the same as that found in the statistical surveys reported in the literature.

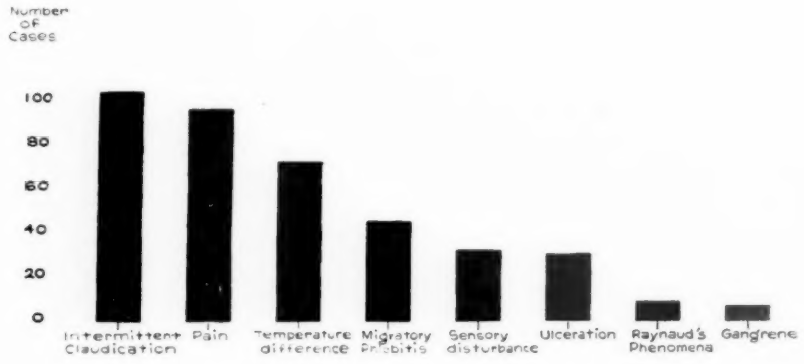

Fig. 3.—Symptoms on admission of patients with thromboangiitis obliterans.

Extent of Involvement.—Thromboangiitis obliterans is a systemic vascular disorder and although its clinical manifestations are generally most noticeable in one extremity, careful examination frequently reveals that blood vessels of other extremities are affected. Fig. 4 illustrates the number of extremities

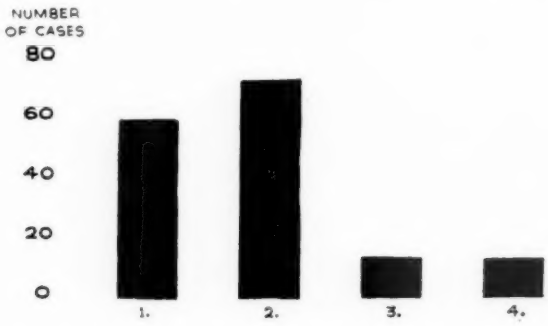

Fig. 4.—Number of extremities involved in patients with thromboangiitis obliterans.

involved in each of the patients. In 62.5 per cent two or more extremities were involved. There was evidence that all four limbs were involved in 13 patients (7.4 per cent). Despite the widespread character of the involvement, visceral

manifestations were rare. In three cases, attacks of precordial pain suggested disease of the coronary arteries. One patient who had suffered from thromboangiitis obliterans of the peripheral arteries for many years developed quadriplegia and other neurological manifestations which indicated that the cerebral vessels probably had been affected.

DIAGNOSTIC PROCEDURES

In addition to a complete history and physical examination in which particular attention was paid to clinical evidence of vascular disorders, certain special procedures were employed in order to establish the diagnosis of thromboangiitis obliterans. Constant temperature rooms were available in each of the vascular centers and also equipment for accurate measurement of skin temperatures and for the determination of oscillations from peripheral arteries. Fig. 5 gives the

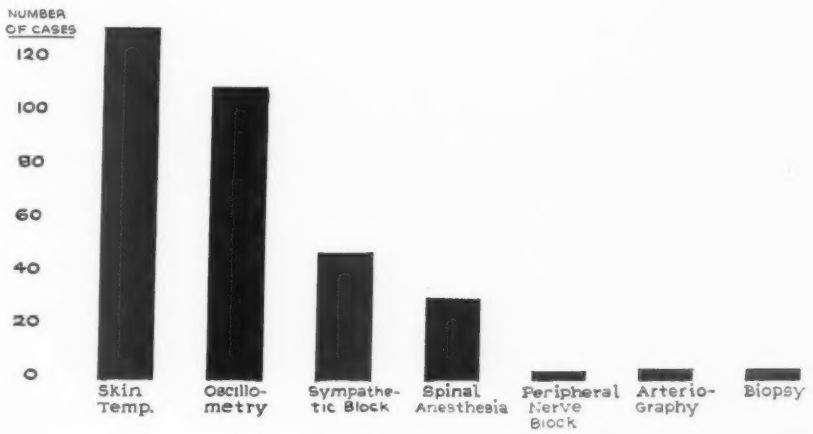

Fig. 5.—Number of diagnostic procedures employed in patients with thromboangiitis obliterans.

total number of special examinations conducted on the patients. Skin temperature studies and oscillometry after release of vasomotor tone by reflex vasodilatation, paravertebral injection of procaine, spinal anesthesia, or peripheral nerve block were especially useful in disclosing early involvement of the peripheral arteries and in the selection of patients for sympathectomy. Radiography after the intra-arterial injection of thorotrast was employed in four patients in whom early involvement of the vessels was suspected. The peripheral pulses were normally present in each of these patients. Arteriography demonstrated, however, that the circulation through these vessels was maintained by means of collateral vascular channels. Biopsy of the affected vessels substantiated the diagnosis in four other patients.

TREATMENT

It is generally agreed that no form of therapy for thromboangiitis obliterans is of use unless the patient completely stops smoking. In the analysis of therapy, therefore, primary consideration is given to this subject.

Smoking.—Ever since Erb[2] called attention to the close relationship between smoking and endarteritis, this aspect of the problem has been the subject of many clinical and scientific observations. Silbert,[3] who has followed for over ten years 100 patients with thromboangiitis obliterans who gave up smoking completely, and who have shown absolutely no progression of the disease, has concluded that the disease "is caused by smoking in individuals constitutionally sensitive to tobacco." On the other hand, Homans[1] has stated: "There is no question that tobacco smoking has a decidedly bad influence upon the course of the disorder, but this does not imply that it necessarily is a cause." Although Silbert[3] maintains that in his experience with 1,300 cases of thromboangiitis obliterans he has observed no case in patients who never had used tobacco, Horton[4] has found the disease present in sixty-eight nonsmokers of a total of 948 cases. Four patients in the present series did not smoke.

Whatever may be the etiologic relationship between smoking and endarteritis, it is generally agreed that abstinence from smoking is mandatory. As Allen[5] has remarked, "It is apparent that it is largely useless to treat patients who continue to use tobacco." Homans[1] has emphasized this fact: "Above all, if he will not abandon tobacco smoking, his disease will almost necessarily persist and indeed will probably be aggravated."

Specific information was obtained on this phase of the subject from the vascular centers on ninety-three patients with thromboangiitis obliterans. Of this number seventy-seven patients stopped smoking completely. Persistence of the disease was noted in two patients. By comparison, in the group of sixteen who admittedly continued to smoke, progress of the vascular obliteration was observed in eight patients.

In this discussion of the relationship between smoking and thromboangiitis obliterans, it may not be amiss to quote the opinions expressed by officers who have directed the medical investigations and care of large groups of patients with this condition in the vascular centers. Major Kahn, of Ashford General Hospital, wrote: "Our experience with the use of tobacco is as follows: While not the cause of thromboangiitis obliterans, smoking is a very aggravating factor. Unless the patient stops smoking completely, no form of treatment, including sympathectomy, is of benefit. Recurrent migratory phlebitis has disappeared with the cessation of the tobacco habit alone. Wounds and gangrenous areas have cleared rapidly, and rest pain has considerably improved when tobacco was stopped. Following sympathectomy, the patients who still smoked complained of pain which was quickly relieved when the habit was stopped. Gangrenous areas were slow in healing and demarcating when the use of tobacco was continued after sympathectomy. Gratifying results were noticed when smoking was stopped."

Major Abramson, of Mayo General Hospital, stated: "It was definitely felt that no medication would be of any value if the patient was not abstaining from smoking. When the diagnosis of thromboangiitis obliterans was made on a patient, the nature of the disease was thoroughly discussed with him and the dangers of continuing to smoke were graphically illustrated to him by showing him the extremities of patients in an advanced stage of the disease. Most of the patients, when informed of the relationship of smoking to the progress of the disease, stated that they would abstain completely. However, in a number of instances it was subsequently brought to our attention that they had not been too serious in their pledge."

As Silbert[6] has remarked: "It is an extraordinary fact that some men will not stop smoking even when repeatedly warned that failure to do so will result in the loss of their extremities." At DeWitt General Hospital considerable attention was paid to this "extraordinary fact." What follows may explain, in part, the failure of many soldiers with thromboangiitis obliterans to give up the use of tobacco.

The majority of patients with thromboangiitis obliterans have passed through many medical installations before arriving at one of the vascular centers. When the diagnosis of vascular disorder is first suspected the patient is generally told by the medical officer that he should "stop smoking" or "cut down on tobacco," but the importance of complete and permanent abstinence is not sufficiently stressed. In most instances the patient does originally resolve to stop but subsequently often resumes smoking. With each successive resolution and failure it becomes more difficult for the individual to stop smoking. Horton[4] quotes Mark Twain to the effect that "he knew all about stopping smoking as he had done it hundreds of times." It is regrettable that many patients with thromboangiitis obliterans are doomed because of their inability to abstain from the use of tobacco.

Rather than to adopt a defeatist attitude toward the problem on the basis that each patient must decide the matter for himself, we have followed the suggestion of Homans,[7] that "the individual should *know* that he will never smoke again." In order to accomplish this end, the patient is carefully instructed to *keep on smoking* until two objectives are realized: (1) until the diagnosis of thrombogangiitis obliterans is irrefutably made and (2) until the patient has had time to consider the matter thoroughly and completely and has come to "know" that he will never smoke again. In other words, the first time that the individual stops smoking is the one time most likely to be successful. The diagnosis of thromboangiitis obliterans must be unquestionable and the patient must be convinced in his own mind of the necessity of stopping. Time is required for both of these facts to be established. As soon as there is no alternative but to stop, the patient quickly adapts himself to the inevitable.

During the earlier period of total abstinence, it has been found helpful to use various types of adjuvants, such as sedatives, occupational therapy, and especially group suggestion. The patients receive considerable help from being segregated into a nonsmoking ward where they are given special privileges.

Under this aggressive policy the proportion of patients who have successfully stopped smoking, at least temporarily, has greatly increased. Of thirty-nine successive cases on the Medical Vascular Section at DeWitt General Hospital, there were only two patients who failed: a 92 per cent success. Much, of course, depends upon the personal relationship between patient and medical officer. Horton[4] estimates that, of those who stopped smoking, 50 per cent resumed the habit. It is unfortunately likely that many of our patients will return to the use of tobacco after separation from the service.

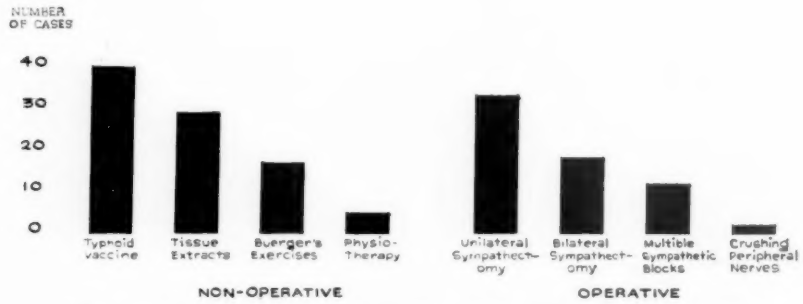

Fig. 6.—Forms of treatment in patients with thromboangiitis obliterans.

The various forms of medical and surgical treatment used in patients with thromboangiitis obliterans are summarized in Fig. 6. Therapy was divided into operative and nonoperative.

Nonoperative Treatment.—Typhoid vaccine was administered intravenously in amounts just sufficient to produce malaise with moderate fever (up to 102°F.) but not enough to cause a chill. Provided that the patient had entirely stopped smoking, excellent results were obtained from this method of therapy.

Tissue extracts including Padutin, Depropanex, and pancreatic tissue extracts were injected by the intramuscular route with improvement in ability to walk in 50 per cent of the patients.

Buerger's exercises and *physiotherapy*, including intermittent suction and pressure and intermittent venous occlusion, were employed in numerous cases but the results were not striking.

Operative Treatment.—Sympathectomy was the treatment of choice in selected cases. Thirty-three of the 160 patients with thromboangiitis obliterans were subjected to unilateral operation; in eighteen patients bilateral resection of the sympathetic ganglia was performed. Sympathectomy of three extremities was done in two of the patients.

Selection of patients for sympathectomy was made on the basis of clinical evidence of increased vasomotor tone and the response of the blood vessels to temporary inhibition or paralysis of vasomotor tone following sympathetic block or spinal anesthesia. In twelve patients treatment consisted in repeated

blocking of the lumbar sympathetic ganglia with procaine. Crushing of the peripheral nerves for the relief of intractable pain was employed in only two patients.

Good results followed sympathectomy at each of the centers. Ulcers healed, there was relief of rest pain, and the patient's ability to walk was improved. Of thirty-four patients reported from two of the centers, failure to improve was noted in only three patients. Amputation of the leg was necessary in two of these patients. It is significant that all three of these patients continued to smoke. Minor amputations were performed in twelve of the remaining 31 patients.

Disposition.—Only three patients in this series were returned to general duty. An additional twenty-one were sent back to limited duty. The remainder were separated from the service either by retirement or by certificate of disability for discharge.

DISCUSSION

The fact that thromboangiitis obliterans was generally observed in the vascular centers in its earlier stages may have been due to the fact that individuals suffering from disorders of the peripheral circulation, especially those that would interfere with marching, were excluded at the original physical examination. Jahsman and Durham[8] have reported on the recognition of thromboangiitis obliterans in draftees. It is therefore probable that in most cases in this series the disease commenced during the period of service in the Armed Forces. No evidence was obtained that military service aggravated the condition. The greater awareness of the medical officers during World War II of the problem of vascular disorders of the extremities and the existence of vascular centers where special diagnostic and therapeutic measures were available made for earlier recognition of thromboangiitis obliterans. The small number of cases in which a major amputation of the extremity was necessary casts a more hopeful light on the therapy of this condition.

SUMMARY

The diagnosis of Buerger's disease, thromboangiitis obliterans, was made in 274 of 3,778 patients admitted to the vascular centers of the United States Army General Hospitals. Except for the fact that the condition was generally seen in its earlier stages, its manifestations were not essentially different from those observed in civilians. Intermittent claudication was the initial symptom in two-thirds of the patients. The average duration of symptoms before admission was 21.9 months. All the patients were men and only 20 per cent were of the Jewish race. The diagnosis was made in seven Negro patients. Ninety-two per cent of the cases were in the age group of 26 to 40 years. Blood vessels in two or more extremities were found to be involved in 62.5 per cent of the patients. Oscillometry and the measurement of skin temperatures in a constant temperature room after blocking the sympathetic vasoconstrictor impulses helped in making the diagnosis and in planning treatment. Chief emphasis was placed on complete

abstinence from smoking. Sympathectomy was the treatment of choice in those cases which gave clinical evidence of increased vasomotor tone. Good results were obtained, but only in those patients who abstained completely from smoking.

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THE INFLUENCE OF VITAMIN B_1 DEFICIENCY ON THE PYRUVATE EXCHANGE OF THE HEART

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THE normal heart absorbs both glucose and lactate from the blood stream,[1] substances that must finally be oxidized or converted to glycogen. The influence of the heart on pyruvate, the precursor of lactic acid, has not been studied. It is generally accepted that thiamine is necessary for the utilization of carbohydrate, because that vitamin is required for the oxidation of the carbohydrate split product, pyruvate. In vitamin B_1 deficiency, therefore, pyruvate accumulates and lactate does so even to a greater extent, frequently in a definite ratio to pyruvate.[2] It has been generally assumed that hyperpyruvemia is a result of a decreased ability of all tissues of the body to utilize pyruvate. In the present investigation, the pyruvate exchanges of the heart were examined in animals suffering from vitamin B_1 deficiency and compared with observations made on the heart of adequately nourished animals.

METHOD

Two groups of dogs were studied: the first was maintained on an adequate diet before the cardiac pyruvate exchanges were determined; the second was fed a mixture containing all known elements required to form a complete diet with the exception of vitamin B_1.[2] The cardiac metabolism in the second group of dogs was examined in different stages of thiamine depletion, as indicated by presence of neurological or other earlier avitaminotic changes, such as gastrointestinal disturbances. For both groups the final experimental procedures were the same. Each dog was anesthetized with pentobarbital and the trachea cannulated. After the animal was placed on artificial respiration, the sternum was split and the pericardium slit to expose the heart. Blood samples were drawn simultaneously from the coronary sinus and the femoral artery. From a 3.0 c.c. syringe, 2.0 c.c. of blood were expressed into ice-cold trichloracetic acid for pyruvate determinations,[3] 1.0 c.c. into Somogyi solution for sugar[4] and lac-

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tate determinations.[5] Arteriovenous differences equal to or greater than 4.0 mg. per cent of glucose, 1.1 mg. per cent of lactate, and 0.12 mg. per cent of pyruvate are considered significant.

Electrocardiograms were taken, using the three standard leads, at the beginning of the experiment with the animals on an adequate diet and again one or two months later before the animals were placed on a vitamin B_1-deficient diet. Further records were made after three weeks of thiamine deficiency and at the time the animals were sacrificed, both before and after pentobarbital anesthesia.

RESULTS

In Table I are presented the number of observations in which the heart added pyruvate, lactate, and glucose, made no significant changes in their levels, or absorbed these substances from the blood stream. The results are subdivided under three headings: those obtained in the animals on adequate diet, B_1-deficient animals examined before neurological signs developed, and B_1-deficient animals with acute neurological signs. The influence of the heart on the pyruvate exchanges is brought out even more clearly in Table II, in which the first column shows the average of all observations in which pyruvate was absorbed by the heart and the second column shows the average quantity liberated from the heart. The third column presents the average effect for all observations and

TABLE I. EFFECT OF HEART ON PYRUVATE, LACTATE, AND GLUCOSE IN CORONARY CIRCULATION

	HEART		
	ADDED (+)	NO CHANGE (0)	ABSORBED (−)
A. The Normal Exchanges of the Heart			
Pyruvate	1	8	12
Lactate	2	4	7
Glucose	6	5	7
B. Cardiac Exchanges in Vitamin B_1 Deficiency With Neurological Signs			
Pyruvate	18	7	1
Lactate	3	6	15
Glucose	7	10	7
C. Cardiac Exchanges in Vitamin B_1 Deficiency Before the Development of Neurological Signs			
Pyruvate	0	0	11
Lactate	0	0	11
Glucose	2	5	4

(+) Number of observations in which substance was added to blood; (0) number in which there was no significant change; and (−) number in which substance was absorbed by the heart.

TABLE II. CARDIAC PYRUVATE BALANCE

	ADDED (+)	ABSORBED (−)	BALANCE*
Normal	0.21 (1)	0.72 (12)	−0.66 (13)
No neurological signs	0.00 (0)	0.82 (11)	−0.82 (11)
Neurological signs	0.51 (18)	0.26 (1)	+0.47 (19)

Figures in parentheses indicate number of observations.
(+) Average of all observations in which pyruvate was added to the blood stream; (−) average of all observations in which pyruvate was absorbed by the heart.
*Average of all significant observations.

shows that the normal heart absorbs pyruvate. The heart of animals exhibiting acute neurological symptoms poured pyruvate more consistently than lactate into the blood stream. On the other hand, the heart of dogs which did not show neurological lesions, with one exception, revealed a picture closely allied to that of the normal animal. The one exception was an animal given 2.0 mg. of thiamine intramuscularly when symptoms of acute vitamin B_1 deficiency were precipitated. This dose did not reverse the neurological signs, although it was adequate to cause the heart to absorb pyruvate from the blood.

In regard to the correlation of electrocardiographic findings with pyruvate balance and neurological signs, the following statements may be made: (1) In the two dogs which did not show acute neurological signs nor any reversal of the normal cardiac pyruvate balance, the electrocardiograms remained essentially unchanged except for variations in rate. (2) In five dogs exhibiting pyruvate output by the heart, there were definite T-wave changes in the electrocardiogram, the T wave being either inverted or diphasic. These five dogs all showed definite neurological signs. In one dog with diphasic T waves, the pyruvate results were not conclusive and neurological changes were absent. (3) Three dogs had definite T-wave changes and neurological alterations, but biochemical studies were not obtained.

DISCUSSION

The present observations not only confirm for the normal heart the absorption of glucose and lactate from the blood stream, but reveal that pyruvate is also extracted from the coronary blood. The heart possesses a greater blood supply than skeletal muscle and accordingly receives more oxygen per weight of muscle. That organ, therefore, not only oxidizes all the carbohydrate split products formed within it, but also utilizes some poured into the blood stream by other organs. The present theories of carbohydrate metabolism postulate that pyruvate, formed according to the Embden-Meyerhof scheme from the breakdown of glycogen to pyruvic acid, is oxidized to water and carbon dioxide with the catalytic aid of vitamin B_1.[6] In a thiamine-deficient animal, the heart loses the ability to oxidize pyruvate and that substance, along with lactate, its reduced form, accumulates in the blood stream. Unlike the effect of vitamin B_1 deficiency on the pyruvate balance of liver, intestine, and skeletal muscle,[7]

in the heart a reversal of the normal pattern occurs. In view of the different actions observed in the heart and other organs, it would seem that an important source of the hyperpyruvemia observed in vitamin B_1 deficiency is the heart.

This cardiac effect has clinical significance, especially when we recall that, at least in the present observations, the appearance of neurological signs was accompanied by an outpouring of pyruvate from the heart. The influence of this abnormal metabolism is observed not only functionally in the changes in the electrocardiogram and the dilated heart, but may also be accompanied by morphologic alterations.[8] It is interesting that cardiac failure is also associated with an abnormally high pyruvate concentration in the blood[6] and that the heart in experimental coronary occlusion releases lactate into the blood stream.[10]

No electrocardiographic changes of any significance were noted before the dogs showed definite neurological signs of vitamin B_1 deficiency. After these signs were exhibited, the electrocardiograms did contain changes involving mainly the form of the T wave. Since an outpouring of pyruvate was found to be associated with T-wave changes, the cardiac pyruvate metabolism may be one of the factors determining the T-wave form. These observations suggest that for the minor unexplained T-wave changes commonly found in clinical cases, the possibility of a thiamine deficiency must be considered.

SUMMARY AND CONCLUSIONS

Five dogs were studied for the normal cardiac exchanges of pyruvate, lactate, and glucose and eleven animals with vitamin B_1 deficiency were examined. In most instances pyruvate was removed from the blood in the normal animal and also in animals without neurological lesions. In the latter, the removal was even more marked, perhaps because of the higher level of pyruvate in the arterial blood. In the animals with neurological symptoms, the heart poured additional pyruvate into the blood stream despite the hyperpyruvemia. The inability of the heart to absorb pyruvate is, therefore, one of the factors increasing the pyruvate level in the blood in vitamin B_1 deficiency.

Many of the animals with vitamin B_1 deficiency exhibited T-wave changes. These alterations in the form of the T wave were usually associated with an outpouring of pyruvate from the heart and occurred most consistently in animals which exhibited neurological signs. These observations lead to the suggestion that in patients who exhibit T-wave abnormalities, vitamin B_1 deficiency should be suspected as an etiologic factor.

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PATHOLOGY OF THE MITRAL VALVE IN THE OLDER AGE GROUPS

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ABNORMALITIES of the mitral valve are frequently encountered in necropsies of elderly subjects. In the earlier decades of life, the interpretation of these lesions is not difficult. In older individuals, however, there is frequent difficulty in explaining their pathogenesis. In the younger groups, the pathologic changes are usually the result of inflammatory lesions, while in the older groups the origin of the old scarred and degenerative processes which are found is not always apparent. Pathologists are frequently asked whether a given lesion in the mitral valve is of rheumatic or arteriosclerotic origin. This question presupposes that there are rigid criteria or differentiating these changes and fails to take cognizance of the fact that, in the older age groups, degenerative lesions are not infrequently superimposed upon inflammatory ones. The differentiation of these two types of lesions has its limitations even microscopically.

In order to survey the types of lesions in the older age groups, we selected 200 consecutive necropsies performed upon patients at Goldwater Memorial Hospital. This is a hospital for chronic diseases and the large majority of our patients fall into the older age groups. We wish to emphasize that our figures refer only to the patients in this hospital and probably do not have any statistical bearing upon the occurrence of mitral lesions in the general population, since the proportion of patients with cardiovascular disease in this hospital is large. An attempt was also made to correlate the pathologic material with the clinical records.

CRITERIA

For the purpose of our study, each of the valves was placed in one of the following categories:

I. Normal valves
II. Abnormal valves without evidence of inflammatory changes
III. Abnormal valves of inflammatory origin
    A. Nonrheumatic
    B. Rheumatic
        1. Acute
        2. Chronic
        3. Healed

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Normal Valves.—A valve was considered normal if the leaflets were thin and flexible, the chordae thin and delicate, and the ring of normal size and consistency. Some valves whose leaflets were described as "slightly thickened" were also placed in this category. Since no absolute standard exists for the normal thickness of a valve at any age, it was felt preferable not to draw too fine a conclusion from the gross appearance of a valve regarding its deviation from the normal. Gross and Kugel[1] found that, with advancing age, progressive changes, including collagenous and elastic thickening, develop in the valves of the heart. This factor must be considered when dealing with heart valves of patients in the older age groups.

Abnormal Valves Without Evidence of Inflammatory Changes.—This term was used to describe those valves which were considered abnormal but which failed to show microscopic evidence of inflammatory change. Generally the involvement was more of the ring region than of the valve itself. The valve leaflets varied in appearance. Sometimes they were delicate, but more often they showed some thickening or deposition of atheromatous material. In the ring region, the atheromatous material was nodular, although occasionally it was found to involve the entire base of the valve and to form a ring at the orifice. Sometimes the foreign material was obviously calcific. In most cases, no appreciable narrowing of the valve orifice was seen, but in two cases an actual stenosis was found. Microscopically, collagen thickening, hyalinization, lipoid deposition, and calcification were frequently encountered.

Strictly speaking, a congenitally abnormal valve would be placed in this category. We had only one case in which this consideration arose. This was the case previously described by us under the title of "The Tetralogy of Fallot."[11, Case 1] This patient had a congenital abnormality of the pulmonic valve which subsequently was involved by a rheumatic process. The mitral valve which showed an inflammatory process was not congenitally abnormal, and therefore this case is included in the rheumatic series.

Abnormal Valves of Inflammatory Origin—Nonrheumatic.—This group would include specific conditions such as acute and subacute bacterial endocarditis, disseminated lupus erythematosis, and terminal endocarditis. Actually, none of our cases were placed in this classification. Accordingly, all valves of our series which showed inflammatory changes were placed in one of the rheumatic categories.

Abnormal Valves Due to Acute Rheumatic Involvement.—Valves placed in this classification showed an acute valvulitis with the presence of acute granulation tissue including fibrin, inflammatory cells, and newly formed blood vessels. These deposits wese found in the valve substance itself or, more frequently, they constituted verrucae which projected from the surface of the valve over an underlying valvulitis. Aschoff bodies were only rarely found in the myocardium; in general, the inflammatory lesion of the valve was not accompanied by a corresponding lesion in the myocardium. The degree of inflammatory response varied but in most cases was not extensive. The acute lesions were all seen in valves which had previously been inflamed.

Abnormal Valves Resulting From Chronic Rheumatic Involvement.—This group included those valves which showed inflammatory changes of a chronic nature. The valves were thickened, fibrotic, and hyalinized; some were calcified. The essential change, however, was the presence of a moderate to severe inflammatory infiltration consisting mainly of lymphocytes, diffusely and focally distributed throughout the valve substance, as well as definite vascularization of the valve. The outstanding lesion, therefore, was a persistent cellular inflammatory process.

Abnormal Valves Resulting From Healed Rheumatic Involvement.—The basis for this diagnosis was principally the finding of vascularization and fibrosis of the valve of long standing. A slight cellular infitration occurring as scattered cells at times accompanied these lesions. The question of the presence of blood vessels in the normal human valve has been considered by many writers.[2-7] The consensus is that blood vessels are not found in the normal human valve on microscopic section. There are still some differences of opinion concerning the value of injection methods for demonstrating vessels in a valve; the majority of pathologists believe that microscopic examination is superior to the injection method. When vessels are present in a valve and show, in addition, irregularity and thickening of their walls, irregularity of their lumens, perivascular fibrosis, and cellular increase in their vicinity, their inflammatory origin is assured. Since vascularization of the mitral valve occurs in only a few specific conditions other than rheumatic disease and since these are not applicable to our cases, we have considered all vascularization to be an indication of rheumatic involvement of the valve. The only exception made was for the finding of a few vessels in the proximal portion of the valve where there was extension into it of the auricular myocardium. When found in a sclerotic valve, such vessels were not considered to be abnormal, even if their walls were slightly thickened; it was assumed that such sclerosis had occurred simultaneously with a comparable process in the valve and was not due to an antecedent inflammatory process. The presence of blood vessels alone was considered to be significant only if the vessels were found in the valve proper; the finding of a few vessels in the valve ring was not considered to be diagnostic of an inflammatory process. Had we included these latter instances in our rheumatic series, our figures would have been higher than they are. The microscopic appearance of the other valves was occasionally taken into consideration in those borderline cases where the differentiation was difficult, as was the appearance of the pericardium and the auricular endocardium. Generally, however, each valve was evaluated on the basis of its own appearance.

It is in healed rheumatic valves particularly that a degenerative process, consisting of hyalinization, atheroma, and calcification, may be superimposed and may mask the original disease. Careful attention to the microscopic picture, however, will usually show the underlying ancient inflammatory process. Vague outlines of hyalinized blood vessels merging into the general fibrous mass may sometimes be seen. Some information may be obtained from the fibrosed tissue itself. Hyalinized fibrous tissue of inflammatory origin is more of a true scar

and its bundles are more likely to assume a crisscross arrangement, whereas fibrosis due to simple collagen condensation is more likely to be linear. It must also be pointed out that it some instances of healed rheumatic endocarditis, all traces of a former inflammatory process may have disappeared and only a thickened fibrotic valve may remain.

MATERIAL

Of the 200 consecutive autopsies studied, twenty-three were unsuitable either because of insufficient data or because the patients were below the required age of 40 years which we had set as the lower age limit. The remaining 177 cases furnished the material for our analysis.

The classification of the mitral valves of the 177 cases is shown in Table I.

TABLE I. LESIONS OF THE MITRAL VALVE

I. Normal valves	96
II. Abnormal valves without evidence of inflammatory changes	49
III. Abnormal valves of inflammatory origin	32
A. Nonrheumatic	0
B. Rheumatic	32
1. Acute	7
2. Chronic	8
3. Healed	17

	MALE	FEMALE	TOTAL	%
Normal	68	28	96	54
*Abnormal	44	37	81	46
Total	112	65	177	

*ABNORMAL VALVES

Rheumatic	15	17	32	40
Nonrheumatic	29	20	49	60
Total	44	37	81	

Age and Sex.—The total percentage of abnormal valves was approximately the same in each age group (Table II). This may be explained by the fact that there were relatively more rheumatic valves in the younger age groups and relatively more atherosclerotic valves in the older age groups. There is a tendency for the percentage of rheumatic valves to decrease with advancing years. The persistence of a considerable percentage of rheumatic valves in the older age groups might at first seem strange. However, these figures relate to the finding of any signs of rheumatic involvement even though the inflammatory process may have become healed. The peak of deaths due to rheumatic heart disease

TABLE II. AGE AND SEX OF 177 PATIENTS WITH ABNORMAL MITRAL VALVES

	40-49 YR.			50-59 YR.			60-69 YR.			70-79 YR.			80-89 YR.			90-99 YR.			TOTAL		
	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL
Rheumatic	1	4	5	4	6	10	4	3	7	3	4	7	3	0	3	0	0	0	15	17	32
Nonrheumatic abnormal	0	2	2	4	2	6	11	6	17	8	4	12	8	3	11	0	1	1	31	18	49
Total abnormal	1	6	7	8	8	16	15	9	24	11	8	19	11	3	14	0	1	1	46	35	81
Normal	6	3	9	14	6	20	21	10	31	15	6	21	11	2	13	2	0	2	69	27	96
Total	7	9	16	22	14	36	36	19	55	26	14	40	22	5	27	2	1	3	115	62	177
Per cent rheumatic			31			28			13			17.5			11			0	13	27	18
Per cent total abnormal			43.5			44.6			46			47.5			52			33	40	51	46

was in the fifth decade, but the number of deaths in the sixth decade was not much lower. There were instances of active inflammatory processes even in the eighth decade.

ABNORMAL VALVES WITHOUT EVIDENCE OF INFLAMMATORY CHANGES

In forty-nine (27 per cent) of our series of 177 patients, the abnormalities of the mitral valves were considered to be the result of noninflammatory changes. The findings varied from slight thickening to manifest atheroma and calcification. In the large majority, there was fibrosis and hyalinization of the ring region and, to a lesser extent, of the valve itself. Patchy deposits of lipoid material and small honeycombed areas of vacuolization were found.

Generally, the more deformed valves were of inflammatory origin, while those with ring calcification or atheroma were the result of noninflammatory processes. Of interest is the fact that in the entire series, mitral stenosis was found in fourteen patients. In twelve of these the lesions were the result of rheumatic disease and in only two were they considered to be of noninflammatory origin. A brief description of the latter two cases follows:

Case 362, a man, 72 years of age, died as a result of hepatoma and portal cirrhosis. There was a narrowing of the mitral orifice due to fibrosis and calcification of the mitral ring which was hard, rough, and apparently atheromatous. The chordae tendineae were delicate. The left auricle was moderately dilated. No microscopic evidence of rheumatic involvement was present.

Case 287, a 73-year-old woman, died of bronchopneumonia and hypertensive heart disease. The mitral opening was reduced, the ring was thickened and atheromatous, and the leaflets were slightly thickened. The chordae tendineae were delicate. The left auricle was not dilated. No microscopic evidence of rheumatic involvement was present.

THE RHEUMATIC VALVES

There were thirty-two patients (fifteen men and seventeen women) in whom the etiology of the changes in the mitral valve was considered to be rheumatic disease (Table III). Among these the mitral valves of twenty-nine showed various degrees of thickening of the valve, or of the ring, or of both. In twelve of the thirty-two patients there was definite mitral stenosis (Table IV) and in eighteen combined mitral and aortic lesions. The changes in the aortic valves varied from thickening and slight atheromatosis, which occurred in most of the cases, to aortic stenosis which was present in three patients. In seven patients of the rheumatic series, the mitral lesions were accompanied by tricuspid lesions.

Most of the rheumatic valves showed the usual findings of rheumatic endocarditis, including thickening and shortening of the valve leaflets with rolling of the edges. Old atheromatous nodules as well as recent verrucae were described. Shortening of the chordae tendineae and fibrosis of the adjacent endocardium were observed in most of the cases. Calcification was a frequent finding. Fibrous and atheromatous plaques were mentioned in several instances. Where mitral stenosis was present, the valves were thickened, fibrotic, and narrowed. In the hearts of six patients in whom mitral stenosis was present, there was gross

TABLE III. ANALYSIS OF THIRTY-TWO PATIENTS IN WHOM THE ETIOLOGY OF THE VALVE LESION WAS RHEUMATIC DISEASE

CASE	AUTOPSY NO.	SEX	AGE	HISTORY	MURMURS	GROSS DESCRIPTION OF VALVES			MICROSCOPIC DESCRIPTION OF MITRAL		
						MITRAL	TRICUSPID	AORTIC	RING	PROXIMAL	DISTAL
1	206	M	69	–	0	T, Ver.			H—Mod., V—Occ.	H—Mod., V—Mod.	H—Mod., V—Mod., C—Sl.
2	220	F	53	–	BS	T, St.	T	Ca., a	H—Mod., V—Occ.	H—Mod.	H—Mod.
3	221	M	87	–	AS, BS	T		a, T	Ca.—Mod , V—Mod., C—Mod.	V—Occ., C—Occ.	V—Mod., C—Mod.
4	222	F	60	–	AS	T, St., Ca		a	H—Mod.	H—Sl., V—T	V—T, Mod.
5	239	M	53	–	AS, AD	T St., Ca	T	a	C—Mod., V—Mod.	C—Mod.	H—Mod.
6	241	F	71	–	AS	T Ca.	T	a	Ca.—Mod., V—Mod.	V—Mod.	H—Mod.
7	245	F	57	+	AS, AD	T St.	T	T	C—Mod , V—Mod. T	V—Mod., C—Mod., Ca.—Mod	V—Mod., C—Marked
8	257	M	74	–	0	T			C—Mod.	C—Mod., V—Mod.	V—Mod., C—Mod.
9	260	F	75	+	AS, BS	T Ca.		T, Ver.	V—Mod. T	V—Occ.	H—Mod.
10	263	F	54	–	AS	T St., Ca.		T	Negative	V—Mod., C—Mod.	Negative
11	266	F	62	–	0	T St.		a, T	H—Mod., V—Mod.	V—Mod., C—Mod.	V—Few, C—Few
12	271	F	42	–	AS, AD	T, St., Ca.		T, a	V—Mod., C—Mod., Ca.—Mod	V—Mod , C—Mod.	V—Mod., C—Mod.
13	272	F	62	–	AS	T St.		T, a	Ca.—Mod , V—Few	V—Mod T	V—Mod., T
14	276	M	78	–	AS, AD, BS	T		T a	V—Mod , C—Mod., F—Mod.	V—Mod., C—Mod.	V—Mod., C—Mod.
15	279	M	41	–	AS, AD, BD	T Ver.		T a	C—Few, V—Mod.	C—Mod , V—Mod.	C—Mod., V—Mod.

16	280	F	52	+	AS	T			H—Mod., V—Mod.	V—Mod., H—Mod., Ca.—Mod	H—Mod., V—Sl.
17	285	F	59	—	AI, BS	T, Ca.			Ca.—Mod., V—Many T	V—Mod., C—Few	F—Mod., V—Mod., C—Few
18	307	M	62	—	0	T			V—Few	V—Many, C—Few	V—Mod., C—Few
19	309	F	40	—	MS	T			C—Mod., V—Sl.	C—Few	
20	314	F	59	—	0				V—Mod., C—Mod.	V—Mod., C—Mod.	H—Mod.
21	317	F	42	—	AS, BD	T, St.			C—Few	H—Mod.	V—Few, C—Mod.
22	321	M	85	—	AS, BS	St., Ca.			C—Mod., F—Mod.	V—Few, C—Mod., Ver.	C—Mod., V—Mod.
23	327	M	52	—	AS	T, Ver.			C—Occ.	C—Occ., V—Mod. T	H—Mod., C—Many
24	334	M	65	—	AS			St.	H—Sl., V—Mod.	C—Few, V—Mod. T	H—Sl.
25	340	M	81	—	0	St.		St.	C—Mod., V—Mod.	C—Mod , V—Mod.	C—Occ , V—Occ.
26	343	F	71	—	AS, BS	T, Ca.			V—Mod., Ca.—Mod.	V—Mod., C—Mod.	H—Mod.
27	360	M	53	+	AS, AD, BS, BD		Congenital	Pul.	Ca.—Mod., H—Mod.	H—Mod.	H—Mod.
28	373	F	42	+	AS, AD, BS, BD	St.	St.	T, St.	V—Mod., C—Mod.	V—Mod., C—Mod.	V—Mod., C—Mod.
29	374	M	69	—	0	T, Ver.	T	T	Ca.—Mod., V—Few	Ca.—Mod., V—Mod.	C—Mod., V—Mod.
30	377	M	50	—	0				V—Mod. T.	V—Sl. T	H—Mod., V—Mod. T
31	378	F	79	—	AS	T			H—Mod., V—Mod.	H—Mod., V—Mod.	H—Mod., V—Mod. T
32	381	M	73	—	0	T			V—Many, H—Sl., Ca.—Mod.	H—Mod., V—Mod.	H—Sl., V—Many T, C—Sl.

0, None; BS, basal systolic; BD, basal diastolic; AS, apical systolic; AD, apical diastolic; MI, mitral insufficiency; MS, mitral stenosis; AI, aortic insufficiency; T, thickened; Ver., acute verrucae; Ca., calcification; a, atheroma; H, hyalinization; F, fibrosis; V, vessels; C, cells; Sl., slight; Mod., moderate; Occ., occasional; St., stenosis.

TABLE IV. DESCRIPTION OF THE MITRAL VALVES IN NINE PATIENTS WITH RHEUMATIC MITRAL STENOSIS

NO.	CASE	AGE	SEX	TYPE OF LESION
1	222	60	F	Thickened, calcified valve
2	239	53	M	Thickened, calcified valve
3	245	57	F	Thickened, rolled
4	263	54	F	Thickened, atheromatous, calcified
5	266	62	F	Thickened, atheromatous
6	272	62	F	Thickened, calcified
7	317	42	F	Thickened, fibrotic
8	321	85	M	Fibrotic, calcified
9	340	81	M	Fibrotic, calcified
10	373	42	F	Thickened, rolled
11	220	53	F	Thickened, rolled, calcified
12	271	42	F	Thickened, calcified

calcification. It is of interest that nine of the twelve patients with mitral stenosis were women.

In three patients of this series, the valves were described as being normal on gross examination, but an inflammatory lesion was found microscopically. A brief description of the three cases follows:

Case 314, a 59-year-old woman, died of fat embolism following a bone fracture. The mitral valve showed interstitial valvulitis. The myocardium showed Aschoff bodies.

Case 334, a man, 65 years of age, died of carcinoma of stomach. The mitral valve showed thickened blood vessels and a moderate cellular infiltration in the proximal portion. The aortic valve showed aortic stenosis of moderate degree with fusion of the commissures.

Case 377, a 50-year-old man, died from rheumatoid arthritis and amyloid disease. Both the mitral ring and mitral valve showed a moderate number of vessels which were thickened and merged into a fibrotic valve structure.

Activity of Rheumatic Disease.—In a practical consideration of rheumatic disease of the heart, the question of the presence or absence of activity will arise. Activity is a clinical rather than a pathologic term, although evidence of clinical activity frequently can be substantiated morphologically. Thus, the finding of an acute pathologic lesion characterized by the presence of masses of inflammatory cells and particularly polymorphonuclears, fibrin, or necrotic tissue is evidence of an active process. However, the point at which clinical activity ceases is not one that can be precisely defined histologically. Thus, lymphocytes are seen for a long time in tissues which have no demonstrable evidence of inflammatory activity clinically, as, for example, in arrested tuberculous foci. The same may be true of rheumatic valvular disease. One cannot judge, therefore, the exact clinical response from the observation of the number of cells seen in a lesion; one can merely arrive at some opinion regarding the acuteness or chronicity of the disease from seeing the numbers and types of cells in the lesion. The converse, however, is true; when all inflammatory cells have disappeared, the lesion is undoubtedly inactive.

In the view of the foregoing considerations, we examined the thirty-two cases designated as rheumatic for the presence or absence of cells in the mitral valve, as well as for the finding of a superadded acute inflammation (Aschoff bodies, verrucae, etc.).

In seventeen cases (53 per cent) of the rheumatic series, the mitral valve was in a healed or scarred state. In fifteen (47 per cent), a cellular inflammatory response of varied degree was present. Generally, the cellular collections were not marked and were of the type seen in a chronic, mild, valvulitis. Vascularization and sometimes calcification accompanied the cellular collections. The cells wese chiefly lymphocytes, although histiocytes and fibroblasts were frequently seen. Table V indicates the approximate degree of this involvement.

Among the fifteen patients in whom a cellular reaction was present, there were seven which showed evidence of a more acute lesion.

Case 206, a man, 69 years of age. The mitral valve showed recently organized verrucae.

Case 245, a woman, 57 years of age. The mitral valve showed an extensive cellular infiltrate which contained numerous polymorphonuclear leucocytes.

Case 279, a man, 41 years of age. The mitral valve showed extensive acute valvulitis and recent organizing verrucae.

Case 314, a 59-year-old woman. The mitral valve showed moderate vascularization. The myocardium showed several Aschoff bodies in the vicinity of blood vessels.

Case 327, a 52-year-old woman. The mitral valve showed recent organizing verrucae.

Case 374, a 69-year-old man. The mitral valve showed recently organized verrucae with palisading.

Case 360, a 53-year-old man, died in congestive heart failure. The basic heart lesion was congenital, the Eisenmenger complex. There was also evidence of rheumatic involvement of the mitral and pulmonic valves. The myocardium showed Aschoff bodies.

Accordingly, it can be said that the presence of an inflammatory cellular response was found in 47 per cent of the rheumatic series and that in 22 per cent there was evidence of a more acute lesion; or, more simply, slightly less than one-half of the thirty-two patients with rheumatic disease showed a cellular inflammatory lesion of the mitral valve of varied degree and slightly less than one-quarter showed acute lesions. In two of the latter, in addition to valvulitis, Aschoff bodies were demonstrated in the myocardium.

History of Rheumatic Fever.—Of the thirty-two patients with rheumatic mitral disease, a positive history of rheumatic fever was elicited in only five (Table VI).

A negative history of rheumatic fever in patients in the older age groups is therefore of little help in diagnosis. Of especial interest is one patient (Case 260) who gave a history of "rheumatism" lasting for sixty days at the age of 29 years and who lived to the age of 75; death was the result of carcinoma of the rectum. A loud systolic murmur was present during life. At autopsy was shown deformity of the mitral valve with thickening and nodularity of the mitral leaflets and with chordae tendineae which were shortened and thickened and which bound down the valve.

TABLE V. FINDINGS IN PATIENTS WITH INFLAMMATORY CELLULAR CHANGES OF THE MITRAL VALVE

NO.	CASE	SEX	AGE	HISTORY OF RHEUMATIC FEVER	DIAGNOSIS OF RHEUMATIC FEVER MADE	CLINICAL EVIDENCE OF ACTIVITY	PATHOLOGIC EVIDENCE OF ACTIVITY	GROSS LESIONS
1	206	M	69	0	0	0	Recently organizing verrucae	Thickened, verrucae
2	221	M	87	0	0	0	0	Thickened valve and ring
3	245	F	57	+	+	0	Many cells including numerous polys	Mitral stenosis
4	271	F	42	0	+	0	0	Mitral stenosis
5	276	M	78	0	0	0	0	Thickened
6	279	M	41	0	0	0	Recent organizing verrucae, extensive acute valvulitis	Thickened, verrucae
7	314	F	59	0	0	0	Aschoff bodies in myocardium	Normal
8	317	F	42	0	+	0	0	Mitral stenosis
9	321	M	85	0	0	0	0	Mitral stenosis
10	327	M	52	0	0	0	Organizing verrucae	Thickened, calcified
11	340	M	81	0	0	0	0	Mitral stenosis, calcification
12	343	F	71	0	0	0	0	Thickened, calcified
13	360	M	53	+	+	0	Aschoff bodies in myocardium	Pulmonic stenosis, tricuspid insufficiency
14	373	F	42	+	+	0	0	Mitral stenosis
15	374	M	69	0	0	0	Recent organizing verrucae	Thickened, nodular verrucae

TABLE VI

CASE	SEX	AGE AT ONSET	AGE AT DEATH
245	F	24	57
260	F	29	75
280	F	22	52
360	M	25	53
373	F	32	42

The absence of a positive history, therefore, is usual in older patients with rheumatic disease. Patients who died in the fifth or sixth decade are more likely to give a positive history than those who die later. The former constitute a group in which a correct diagnosis is made during life. Many of the others who die at a more advanced age are undiagnosed or are considered to be cases of arteriosclerotic heart disease.

Physical Examination.—A complete analysis of the physical findings in the rheumatic patients was not undertaken. Consideration was given only to the presence or absence of murmurs. Murmurs were present in twenty-three patients (72 per cent) and absent in nine cases (28 per cent). In two of the patients in whom no murmurs were heard, the valves were grossly normal, though microscopic evidence of rheumatic involvement was present. In five patients in whom no murmurs were heard, the valves were grossly abnormal, the leaflets being definitely thickened. In two of these five patients, the lesion was mitral stenosis: one patient had auricular fibrillation throughout his hospital stay; the other patient was on a surgical service with diabetes and gangrene of the leg and only one examination of the heart was recorded. In four of the nine patients in whom murmurs were not recorded, there was cellular infiltration of the mitral valve which suggested a continuing inflammation. It is apparent that the absence of murmurs does not exclude the possibility of rheumatic valvulitis in patients in the older age groups.

Contribution of Rheumatic Valvulitis to Morbidity and Mortality.—The effect of the abnormal valve on the patient's course was considered. This was most difficult to evaluate since many factors were involved. In fifteen of the thirty-two patients in the rheumatic group, the abnormality of the mitral valve was considered to have contributed to the patients' illness and, in some cases, to his death. This conclusion was reached either because the valvular deformity was such that a dysfunction had apparently been present during life, or because the clinical record, as well as the pathologic findings, indicated the presence of an acute lesion, and particularly one which involved the myocardium. Of these fifteen, ten were in Class III-B-1 (acute rheumatic) and III-B-2 (chronic rheumatic), while five were in Class III-B-3 (healed rheumatic). The implication of these figures is that the influence of acute and chronic rheumatic valvulitis upon

morbidity and mortality was more than twice that of healed rheumatic valvulitis. In more than one-half of the total number of patients (seventeen of thirty-two) the rheumatic lesion was not of clinical significance.

CALCIFICATION

In considering the frequency of rheumatic endocarditis in the older age group, one eventually must face the problem of the atheromatous and calcific valve. That the finding of calcium is not a rarity can be seen from the fact that we found calcific deposits in the mitral valve in 30 per cent of our patients. The deposits were, in some instances, large and easily palpable. In some specimens the deposits encircled the entire valve base; in others they were felt as nodular collections either in the valve ring or in the valve proper; and in still other instances, the calcium was demonstrated only by microscopic study. Our figures for the presence of calcium are undoubtedly too low, since only one or, at most, several sections of the valve were available for study. Whether such deposits are merely an infiltration into the tissue of the valve of extraneous material due to local metabolic disturbances or whether they are the end results of an inflammatory process is a differentiation which is difficult to make on gross examination and not always possible even on microscopic examination. The problem is all the more difficult since we found deposits of calcium without any inflammatory reaction in their vicinity in valves which showed typical rheumatic disease in adjacent portions, while on the other hand we found blood vessels and sparse numbers of lymphocytes around deposits of this material in the valve ring in valves which otherwise showed no signs of rheumatic endocarditis. That calcium by itself does not produce any inflammatory response is seen from the fact that we have seen numerous instances of calcium deposit in heart valves without any accompanying inflammatory reaction whatever. This view has been expressed by Clawson and co-workers.[8]

The deposition of calcium is apparently part of the healing process in rheumatic disease. We have seen well-formed calcium deposits in the valve of a girl of 13 years who died of rheumatic endocarditis. Consequently, one has to bear in mind that the finding of calcium does not necessarily indicate a degenerative lesion alone. In many cases it undoubtedly indicates the end result of a rheumatic process.

Types of Calcium Deposition.—Examination of the valves reveals that calcium is to be found in three well-discernible forms:

1. A granular or dustlike infiltration. This is most frequently seen in the valve proper, although it may occur also in the ring. It is not accompanied by any blood vessel or cellular increase. Occasionally, however, the outlines of blood vessels may be found; the processes appear to be unrelated. This type of calcific deposition is found usually in the valves of old patients.

2. Patches of calcific material in the valve ring sometimes extending for a short distance into the valve itself and sometimes accompanied also by calcification of the adjacent ventricular myocardium. The material appears as sheetlike

deposits. It merges with the adjacent more normal tissues and appears merely to replace tissue that had been previously damaged. Blood vessels do not accompany this type of lesion. Occasionally, such deposits are seen also in the valve proper. These lesions appear to be noninflammatory in origin, although we have seen them in valves that showed definite evidence of a previous rheumatic disease.

3. Patchy deposition in multilocular or honeycombed spaces, accompanied by either blood vessels or cells, or both, and located usually in the valve ring and not infrequently in the valve proper. Such deposits in the valve or ring and accompanied by old granulation tissue are characteristic of healing rheumatic endocarditis. However, we have seen a considerable number of such deposits limited to the ring and fringed by blood vessels, which usually appear to be dilated capillaries, in valves which otherwise showed no evidence of an old inflammation. Occasionally, small numbers of lymphocytes are seen in the vicinity. While we have been suspicious of the possible inflammatory origin of these latter lesions, we have nevertheless not considered such lesions which are limited entirely to the mitral ring as being sufficiently definite to warrant their classification as rheumatic.

We found calcification in fifteen of the thirty-two rheumatic patients (47 per cent) and thirty-eight of the 145 nonrheumatic patients (26 per cent). In ten of the fifteen rheumatic patients, calcification was noted grossly (as well as microscopically), while in five the deposits were seen only on microscopic study. In the thirty-eight nonrheumatic patients, calcification was seen grossly in five, while in thirty-three patients it was demonstrated only microscopically.

To summarize, therefore, calcification with or without vascularization is frequently seen in old rheumatic endocarditis. The multilocular type described is more likely to be of rheumatic origin and to be accompanied by vascularization, lymphocytic infiltration, and fibrosis. Nevertheless, if it is limited to the ring region and is not accompanied by a definite valvulitis, it cannot be assumed to be definitely of rheumatic origin.

DISCUSSION

Lesions of the mitral valve occur with considerable frequency in the older age groups. In our hospital population, 45 per cent of the patients analyzed showed some abnormality of the mitral valve. Such lesions of the mitral valve are either of inflammatory or of noninflammatory (degenerative) origin. At times, degenerative changes may be superimposed upon originally inflammatory lesions. In patients over 40 years of age, rheumatic lesions of the mitral valve are not rarities. In the total series of 177 patients over 40 years of age, such lesions were present in 18 per cent.

In 47 per cent of the rheumatic series, a cellular inflammatory process was demonstrated in the mitral valve. The more extensive and deforming lesions of the mitral valve are, in the large majority of cases, of rheumatic origin: This etiology is especially suggested if the involvement includes the valve leaflets. Cellular reaction, when present, varies in degree. At times it is not marked, but

occasionally it may be accompanied by verrucae and rarely may be associated with Aschoff bodies in the myocardium. The presence of such inflammatory lesions is not limited to any particular age group. Four patients whose valves showed inflammatory lesions were, respectively, 78, 81, 85, and 87 years of age.

The presence of calcification in a valve does not necessarily indicate a degenerative etiology. Fifteen of our rheumatic patients showed calcification and six of nine of our patients with rheumatic mitral stenosis showed the presence of calcium. Calcium by itself does not produce an inflammatory reaction. When calcification is found in the valve proper and is accompanied by blood vessels, inflammatory cells, or both, it is a consequence of an inflammatory process. When calcification is limited to the mitral ring alone and is not accompanied by other evidences of a preceding inflammatory process, a definite rheumatic etiology cannot be assumed.

The rheumatic process is thus long and protracted and not necessarily limited to youth, although its greatest incidence and its most spectacular phases occur then. Cohn and Lingg,[9,10] in their clinical analysis of 12,000 cases, have spoken of an active phase and of a latent phase. The pathologic analysis of our small group of cases agrees with this view. The latent phase may extend for months, or for a great many years, as was the case in some of our patients. The belief that the disease can exist for a short time and be entirely eradicated may be true in some instances. On the contrary, the process may linger on for a long time and be subject to minor exacerbations of which the patient is unaware. Inflammatory foci may apparently become active in a valve without being accompanied necessarily by myocardial lesions. In other instances, the healed lesion may remain for a long time, with or without physical findings, and without shortening the patient's life. Thus, in our series, seventeen patients (53 per cent) with rheumatic disease were more than 60 years of age at the time of their death and three were more than 80 years of age. Most of the patients in this series did not die of rheumatic heart disease. One can perhaps speak of the fulminant, protracted, or comparatively benign forms of this disease and a similarity to tuberculosis may be invisaged. What accounts for this difference of clinical and pathologic course is unknown, but apparently it exists principally in the patient himself and is generally considered to be due to the poorly understood factor, resistance. In short, rheumatic disease is not a respector of age; it prefers the company of youth, but may accompany the host to old age.

SUMMARY AND CONCLUSIONS

1. Disease of the mitral valve occurs with considerable frequency in patients in the older age groups. In consecutive autopsies on 177 patients who were 40 years of age or older at time of death, the mitral valve was found to be abnormal in eighty-one (46 per cent); in thirty-two (18 per cent) the etiology of the mitral valvulitis was considered to be rheumatic. Rheumatic disease was responsible for 40 per cent of the abnormal valves found in this series of patients.

2. The percentage of patients who showed abnormal mitral valves was almost constant (approximately 50 per cent) in each decade after the fourth.

The number in which rheumatic disease was the etiology showed a tendency to decline with advancing years. In our rheumatic series, women predominated.

3. The more extensive and deforming lesions of the mitral valve are likely to be of rheumatic rather than of degenerative origin. Mitral stenosis, including the atheromatous and calcific type, is, in the large majority, rheumatic in origin and is more likely to occur in women.

4. Evidence of a cellular inflammatory process was present in the mitral valve in 47 per cent of the patients in our rheumatic series. Among these there were seven in whom the process was considered to be acute; in two of these, Aschoff bodies were found in the myocardium.

5. Calcification frequently accompanies the rheumatic process and was seen on gross and microscopic examination in 47 per cent of the cases.

6. A positive clinical history was obtained in only a small proportion of the rheumatic cases (15.5 per cent). The clinical diagnosis of rheumatic heart disease is not usually made in older patients. Nine of our patients (28 per cent) showed no murmurs at the time of the clinical examination.

7. Rheumatic disease of the heart of various degrees occurs more often in the older age group than is clinically surmised. In many older patients the condition has a comparatively benign course.

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Clinical Reports

CONGENITAL PAROXYSMAL TACHYCARDIA

Report of Case Recognized Ante Partum

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THE total number of reported cases of paroxysmal tachycardia in infants, newly born or in their first year of life, is not large; there are probably many cases which go unrecognized. In 1941 Hubbard[1] was able to find only nineteen well-established cases in infants under 1 year of age. To these he added nine new cases, six of which he had observed during the course of a single year.

It is not known at what stage of intrauterine life paroxysmal tachycardia first develops. Two cases of paroxysmal tachycardia, recognized prior to birth, have been reported.[2,3] In one the arrythmia was first noted during the twenty-four hours immediately preceding birth and in the other, it was recognized a month prior to delivery. The case to be presented is that of an infant in whom tachycardia was recognized by the attending obstetrician* three months prior to birth at full term.

CASE REPORT

On Jan. 30, 1945, while examining a woman at the end of her sixth month of pregnancy, the obstetrician observed that the fetal heart rate was very rapid. Since the tachycardia, estimated to be 200 to 250 beats per minute, was also present on five subsequent examinations during the next three months, he concluded that the fetus had a paroxysmal tachycardia and so informed the mother one month prior to her delivery.

On April 29, 1945 (2:35 P.M.) he delivered, at St. Luke's Hospital, a full-term white female child weighing 8 pounds and 1½ ounces. Delivery was by forceps control and was uncomplicated. Aspiration with a Dann machine was carried out because of slight delay in respiration. On examination of the child the only abnormality noted was a heart rate of 228 per minute. On the following day the rate was 210 per minute.

An x-ray film of the chest on this day showed cardiac enlargement mainly to the left of the midline. The maximum transverse diameter of the heart measured 5.5 cm. as compared to 9.6 cm. for the maximum internal diameter of the thorax. There was no abnormality of the lungs.

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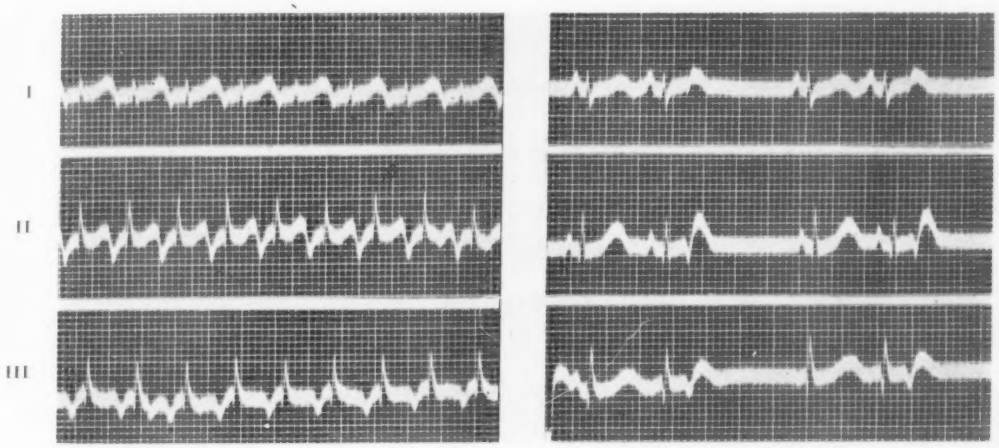
The first electrocardiogram was taken on May 1, 1945, forty-four hours after birth (Fig. 1, *A*). This showed a supraventricular tachycardia arising in the upper portion of the atrioventricular node at a rate of 200 per minute. It was decided to give the infant digitalis, and an electrocardiogram (Fig. 1, *B*) was taken the following day after the equivalent of 0.05 Gm. of digitalis in the form of digifolin had been given intramuscularly. The tachycardia was found to be replaced by sinus rhythm with a rate of 125 per minute. After every second ventricular complex, a blocked P wave was seen. These P waves were sharply inverted in Leads II and III and were of the same general outline as those recorded during the tachycardia. This indicated that the premature auricular contractions were arising at or near the same focus responsible for the tachycardia.



A. *B.*

Fig. 1.—*A*, May 1, 1945, forty-four hours after birth. Supraventricular tachycardia arising in the upper portion of the atrioventricular node. The rate is 200 per minute.

***B*, May 2, 1945, twenty-four hours after intramuscular administration of the equivalent of 0.05 Gm. of digitalis in the form of digifolin intramuscularly. Sinus rhythm has been restored. Following every second ventricular complex there is a nodal extrasystole which is blocked.**

Although digitalis had been effective in stopping the tachycardia, it was evident that the ectopic focus was still active. However, in order to give digitalis a sufficient trial, it was continued for two more days and the next electrocardiogram was made on May 4, 1945. In this record (Fig. 2) the tachycardia was present for the most part but was interrupted occasionally by short periods of normal sinus rhythm.

At this point digitalis was discontinued and the infant was given 10 mg. of quinidine sulfate four times daily on the first day, 20 mg. on the second, and finally 30 mg. four times daily on the third day. This dosage was effective and was considered reliable for stopping the tachycardia and restoring normal rhythm.

On May 9, the parents demanded the infant's release. Her condition was good and the parents were instructed to give quinidine, 30 mg., every six hours. They were taught how to detect the presence of tachycardia by applying the ear over the infant's precordial area. This they readily learned which made it possible to direct them to decrease the number of doses when the tachycardia was not present. After the infant was 2 months old, quinidine was given only on those infrequent days when excitement or prolonged crying precipitated a paroxysm.

On Aug. 14, 1945, when the child was nearly 4 months old, the electrocardiogram (Fig. 3) was normal in all respects and showed a conspicious increase in the voltage of the QRS complexes in all leads.

The child continued to develop normally and at the time of the last examination on Oct. 26, 1945, she weighed 16 pounds and 10 ounces. No quinidine had been used and no abnormal cardiac rate had been noted since the child was 3½ months of age.

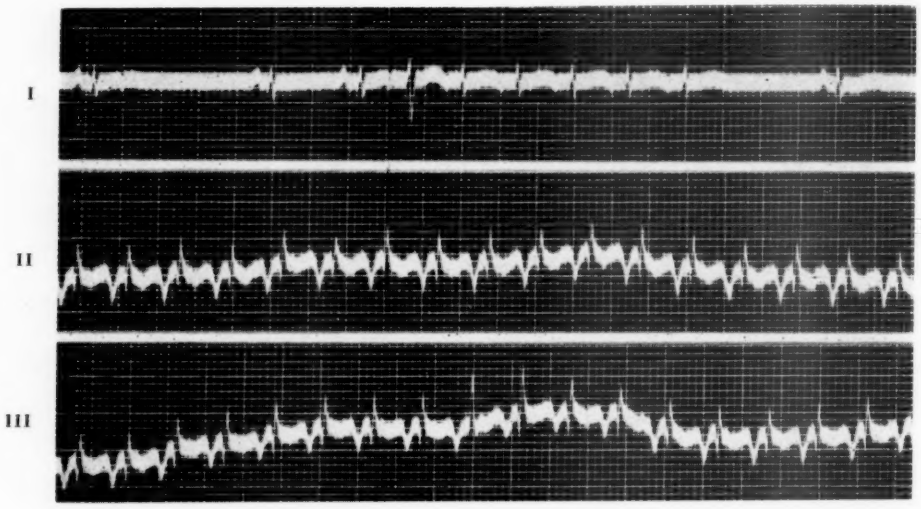


Fig. 2.—May 4, 1945, after the equivalent of 0.15 Gm. of digitalis. The nodal tachycardia is present but intermittent. Superimposed upon the T wave of the first ventricular complex in Lead I there is a small negative deflection representing a premature auricular contraction which is blocked. After the third ventricular complex a similar deflection is followed by a short period of tachycardia with aberration of the first QRS complex of the series.

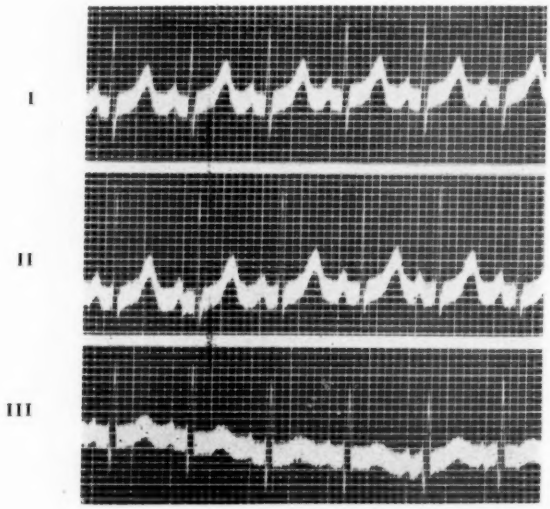


Fig. 3.—Aug. 14, 1945. Normal electrocardiogram.

SUMMARY

A case of congenital paroxysmal tachycardia recognized three months prior to the birth of the child at full term is reported. Single daily doses of the equivalent of 0.05 Gm. of digitalis given intramuscularly on three successive days failed to control the tachycardia. Quinidine sulfate in 30 mg. doses by mouth at six-hour intervals was more effective.

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DIFFUSE SCLERODERMA WITH INVOLVEMENT OF THE HEART

Report of a Case

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SCLERODERMA as it affects the skin has been well known for years but it is only recently that it has become generally recognized as a diffuse systemic disease of the collagenous tissue which may involve all organs containing connective tissue.[1] It, therefore, resembles diffuse lupus erythematosus which at first was recognized as a skin disease and later became known as a generalized systemic disease. In scleroderma, lesions have been described involving the gastrointestinal tract from the buccal mucous membrane to the colon.[2-5] The definite and characteristic involvement of the heart and lungs has been well described by Weiss and co-workers,[6,7] who first used the term "scleroderma heart disease." Lesions have been found in most visceral organs containing collagenous tissue.[8-11]

The reason for reporting this case is that it demonstrates the clinical picture and characteristic pathologic changes of the myocardium, as first described by Weiss, and thus helps to confirm the existence of scleroderma heart disease as a specific clinical and pathologic entity.

REPORT OF CASE

First Admission.—A 23-year-old single woman, who did clerical work, was admitted to the Royal Victoria Hospital on March 10, 1944, complaining of gradually increasing stiffness and tightness of the skin with increasing sensitivity to cold for the past five years. For the last three years there had been a slowly developing brownish pigmentation of the skin and during the last year she had suffered from palpitation, weakness, and dyspnea on exertion.

She first noticed that the skin on the index finger of the left hand became white, then yellow, after which it became stiff and appeared "tight." In the beginning, the lesions subsided with the onset of menstruation and relapsed afterward. The nail of the index finger was lost. The skin became very susceptible to trauma and small, slowly healing ulcers would appear. The process of tightening of the skin extended to all the fingers of both hands, the arms, and the rest of the body and limited movement of the joints. The increasing stiffness of the face interfered with smiling and opening the mouth. Since the appearance of the first lesion, the patient had noted an increased sensitivity to cold which caused the fingers and toes to turn blue and feel numb. This also happened on emotional excitement. The skin pigmentation increased. Six months before admission the patient began to experience cardiac palpitation and weakness on

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exertion and vertigo, especially in the morning. Her appetite was poor and she had lost 16 pounds during the past year. Past and family histories were noncontributory.

Physical Examination.—The patient was a moderately well-nourished woman in no apparent distress. The skin over the entire body appeared thickened and fixed to the underlying tissue. It was tightly drawn over the bony prominence where there were scars of healed ulcers. Small ulcerations were present on the index finger of the left hand and over the lateral malleolus of the left ankle. The fingers and toes were cyanotic and cold, but this disappeared shortly after admission. The only other positive findings were a palpable left lobe of the thyroid, multiple extrasystoles, a blood pressure of 106/75, and a palpable liver and spleen. Special examinations showed a normal blood chemistry and a basal metabolic rate of −9 per cent. Roentgen examination of the hands revealed no changes in the bony texture. A biopsy taken of the skin showed an increase in the thick collagenous fibrils of the corium. The diagnosis was scleroderma and acrocyanosis. Treatment with mecholyl, 10 mg. four times a day, subcutaneously, was initiated for the relief of the acrocyanosis. After a two-week stay in the hospital the ulcers were healed and the patient was discharged.

Second Admission.—On March 13, 1945, the patient was re-admitted, complaining of increasing tightness and pigmentation of the skin. She was able to move her joints only with great difficulty. Sensitivity to cold was greatly increased. She had been forced to discontinue her work four months before admission because of severe weakness and fatigue. Ulcers, which appeared on the nose, the tip of the elbow, and the knuckles during the menstrual periods refused to heal as they had done in the past; instead they gradually increased in size. Palpitation and dyspnea on exertion were more severe. Four days before admission the patient began to have constant pain in the right upper quadrant of the abdomen associated with nausea and vomiting of normal gastric contents. Palpitation increased and she experienced continual mild precordial pain which was relieved by bed rest.

Physical Examination.—The brownish discoloration, marked stiffness, and tightness of the skin had increased. The fingers, arms, and legs were partly fixed in a semiflexed position with indolent ulcerations on the tip of the nose, the elbows, and the knuckles. The chest showed diminished excursions on both sides with harsh breath sounds and scattered coarse râles over both bases posteriorly. The blood pressure was 115/90. The heart was moderately enlarged to percussion, its rhythm was irregular due to frequent extrasystoles, its sounds were diminished in intensity, and a harsh systolic murmur was present at the apex. The liver was 2 cm. below the costal margin and slightly tender. The spleen was not palpable. There was slight pitting edema of the ankles.

Laboratory Findings.—The urine showed a specific gravity of 1.020, a faint trace of albumin, and occasional red and white blood cells. The blood studies and complete hemogram were within normal limits. The basal metabolic rate was −5 per cent. The blood Wassermann and blood Kahn were negative. Blood nonprotein nitrogen, cholesterol, proteins, albumin-globulin ratio, bilirubin, serum sodium, calcium, inorganic phosphorus, and carbon dioxide capacity were normal. An electrocardiogram (Fig. 1) showed an arrhythmia due to extrasystoles, left axis shift, A-V conduction time of 0.24 second, slurred and low-voltage QRS complexes, and diphasic T waves with depressed RS-T intervals in Lead I. The circulation time was 30 seconds and the venous pressure 220 mm. of water. Roentgen examination showed the heart to be definitely increased in size in all its diameters (Fig. 2). There was a dense shadow present at the base of both lungs. A barium meal showed a normal esophagus, stomach, and duodenum. Endocrine assay of the urine revealed a 17 ketosteroid output of only 2.7 mg. per liter in a twenty-four hour volume. (Normal for this laboratory is 12 to 15 mg. per liter.)

Progress and Therapy.—During her stay in the hospital the temperature remained normal. The dietary intake was adequate. Shortly after admission congestive failure increased and a diastolic gallop rhythm appeared. Digitalis was, therefore, given, with a fair response. Because of low ketosteroids the patient was given 10 mg. methyltestosterone three times a day with considerable improvement in the texture of the skin of the face and hands after two weeks' treatment. During the last week in the hospital she suffered from recurrence of substernal tightness and constriction, more evident when excited or emotionally disturbed. The signs of congestive failure

Fig. 1.—Electrocardiogram recorded one week before death, showing abnormalities noted in text.

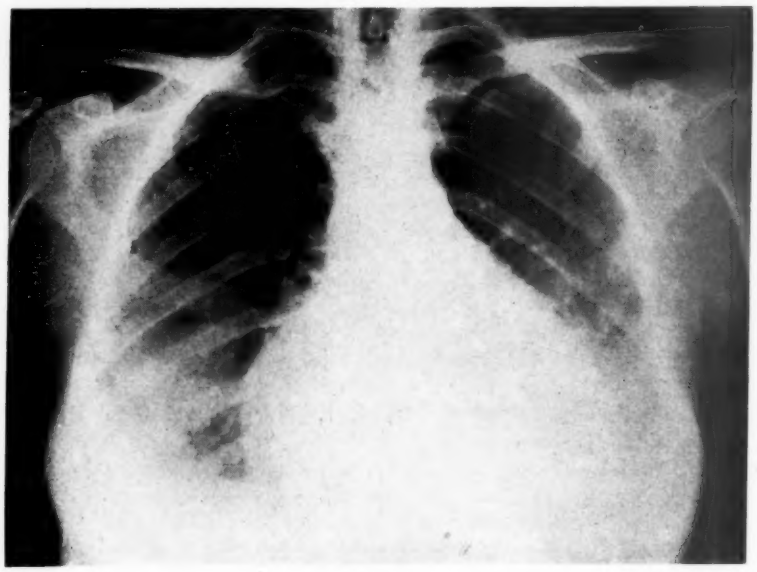

Fig. 2.—X-ray film of the chest showing definite enlargement of the heart with dense shadows present at the base of both lungs.

recurred. Two days before her death she complained of pain in the left chest and the following day expectorated blood-tinged sputum. A friction rub was heard in the left axilla. Her condition deteriorated and she died six weeks after admission.

Post-Mortem Examination.—Necropsy was performed two and one-half hours after death. The following is a summary of the positive findings. The body was that of a well-developed and fairly well-nourished white woman. The skin showed diffuse brownish pigmentation and thickening. Pale patches were present over the right knee and above the pubis. The index fingers were ulcerated and all fingers were semiflexed; they had a clawlike appearance and were difficult to extend. Horny areas were present over both malleoli, over both elbows, and on both buttocks. The free margins of the left ear felt nodular and calcified. The hair was black in color and of the usual female distribution.

The pericardial cavity contained about 300 c.c. of amber-colored fluid. The epicardium showed a white spot on the anterior surface of the left ventricle about 3 cm. in diameter. The heart weighed 295 grams and there was some dilatation of both ventricles. There was a fresh mural thrombus on the endocardium at the apex of the left ventricle. The coronary arteries were patent throughout, and no evidence of obstruction was found down to their finest ramifications. Both pleural cavities were obliterated by dense pleural adhesions and the lungs were subcrepitant on palpation. The peritoneal cavity contained about 200 c.c. of amber-colored fluid. Nothing unusual was noted in the gastrointestinal tract. The liver showed passive congestion.

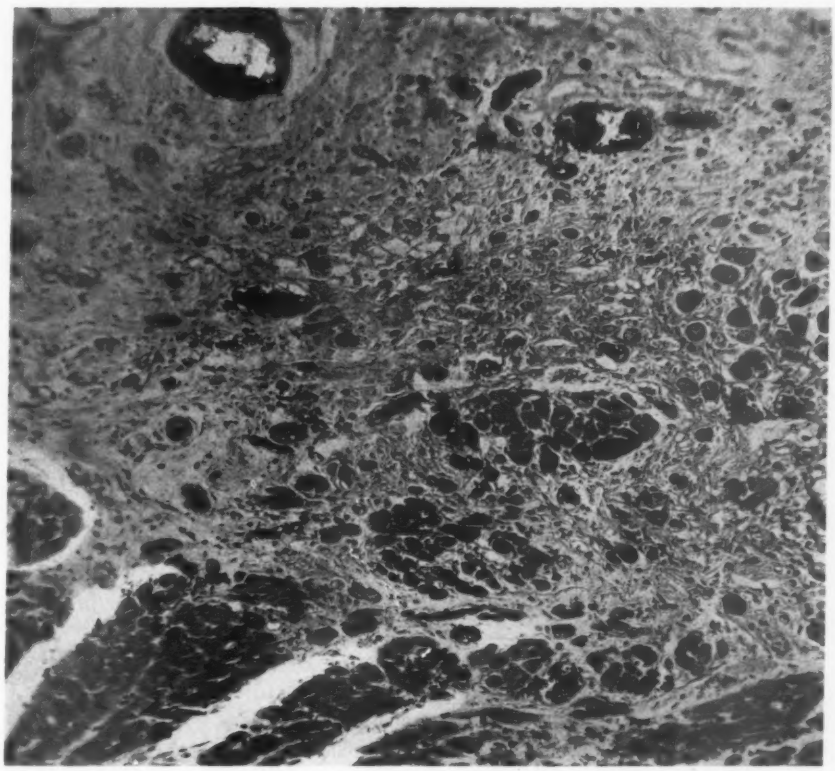

Fig. 3.—Photomicrograph of the myocardium showing a focal area of diffuse fibrosis. There are a few chronic inflammatory cells scattered throughout the fibrous area. Note the islands of intact myocardium surrounded by fibrosis. Some of the muscle fibers in these islands show evidence of varying degrees of degeneration. There are many patent arterioles seen in the section (×110).

The pancreas, adrenals, and spleen appeared normal on gross examination. The right kidney had two small fresh infarcts in the cortex and the left kidney had one. The brain and its coverings appeared normal.

Microscopic Examination.—Focal areas of fibrotic scarring were distributed diffusely throughout the myocardium and did not appear to bear any relation to the vascular tree. In some areas there was infiltration with lymphocytes and monocytes. In places the collagenous bundles were thickened, hyaline, and somewhat eosinophilic; such areas were present in parts of the heart valves. The endocardium and epicardium had areas of collagenous thickening. There was an organizing thrombus at the apex of the left ventricle. Some of the small arteries and arterioles presented thickening of their medial layers with some stenosis of their lumina (Fig. 3). The pleurae were

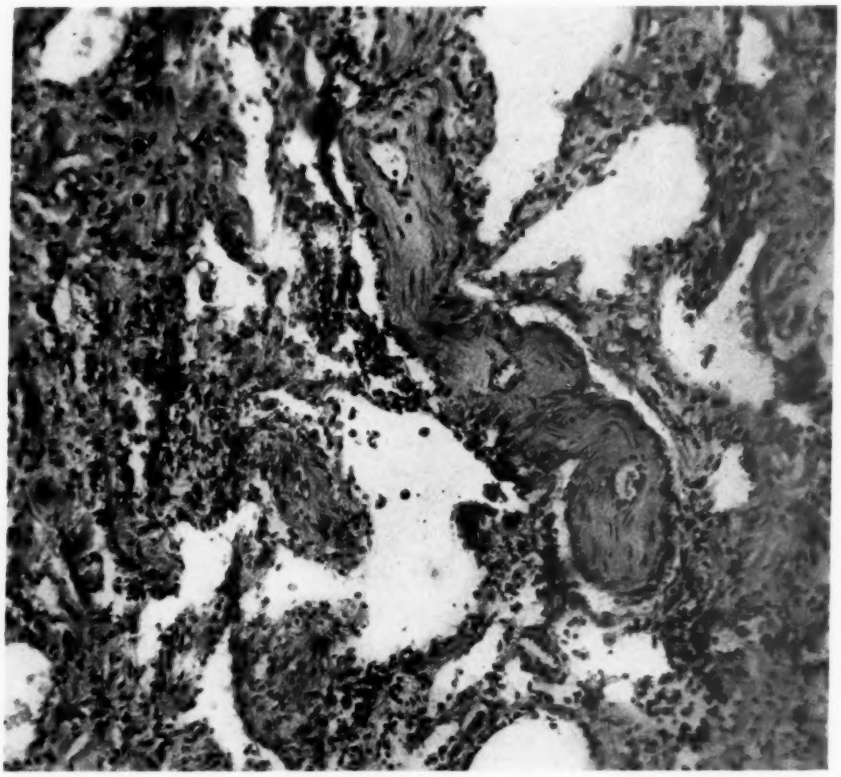

Fig. 4.—Photomicrograph of a section of a lower lobe of the lung showing diffuse fibrotic thickening of the alveolar walls with obliteration of some of the alveolar spaces. Note the adventitial thickening of the arteriole in the center of the section (×110).

thickened by collagenous tissue. In places they showed fibrinoid necrosis as demonstrated by a smudgy red appearance in the hematoxylin and eosin stain and by a red color with Masson's trichrome stain. The lower lobes of the lungs presented a diffuse interstitial fibrosis with obliteration of many alveolar spaces (Fig. 4). The kidneys showed infarction and some "wire loop" lesions of the glomeruli, but the latter were present only to a slight degree. The psoas muscle had irregular patches of hyaline fibrosis. The liver showed evidence of passive hyperemia and fatty infiltration.

In the skin, the epidermis was thinned and the rete pegs were flattened. The melanin content of the basal layer of the epidermis was diffusely increased. Some granules of melanin pigment were seen in the superficial portion of the corium. The superficial dermis showed a fusion

of its components into a smooth hyaline mass. The collagenous tissue in the deeper areas of the dermis was thickened and hyaline but the individual fibers were more distinct than in the superficial layers (Fig. 5). Masson's trichrome stain showed some areas of red staining denoting fibrinoid degeneration of the collagenous tissue.

The lymph nodes had a generalized lymphoid hyperplasia, the capsules and stroma being thickened by collagenous tissue. The larger arteries throughout the body did not show any specific changes. The remainder of the tissues showed no abnormalities.

Anatomic Diagnoses.—These included diffuse scleroderma with acrocyanosis and sclerodactylia, ulceration of the skin of both index fingers, fibrosis of the myocardium, endocardium, and epicardium, dilatation of the heart, mural thrombus of the heart, hydropericardium, embolism of renal arteries, infarcts of kidneys, interstitial fibrosis of lungs, chronic passive hyperemia of liver, ascites, fatty liver, calcification of the left auricular cartilage, and pigmentation of the skin.

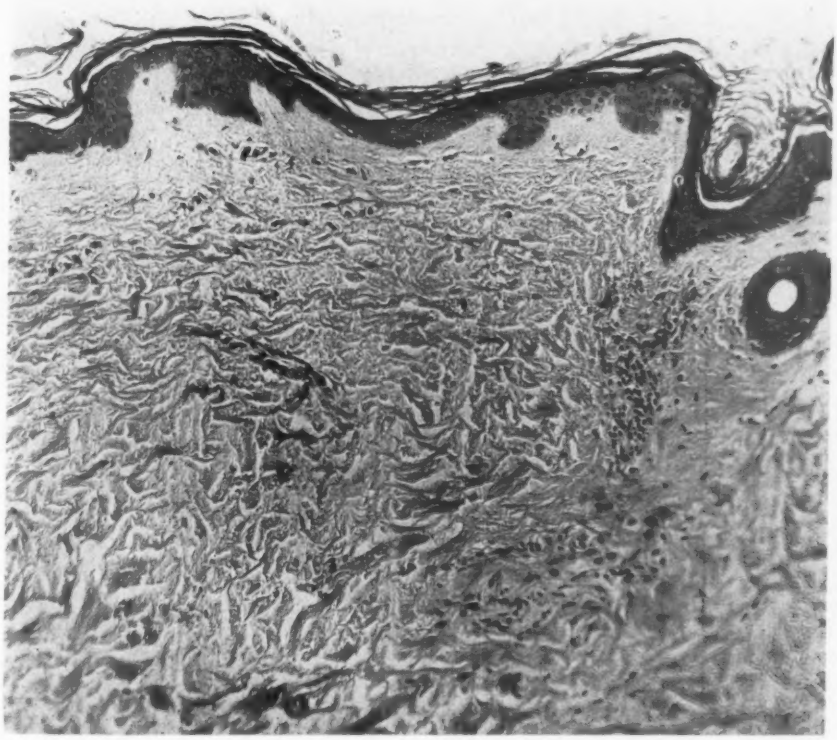

Fig. 5.—Photomicrograph of a section of the skin from the abdomen showing increase in cornification and thinning of the epidermis with flattening of the rete pegs. The collagenous fibers in the superficial corium are diffusely swollen and increased in number. Note the discrete area of lymphocytic infiltration in the corium near a hair follicle (×110).

COMMENT

The early history of this case is typical of scleroderma as it affects the skin. The definite remissions noted with the onset of menstruation and exacerbations afterward, the low ketosteroids, and the favorable response of the skin changes to methyltestosterone seem to favor the theory that an important etiologic factor

in scleroderma is an endocrine dyscrasia. There was no evidence of other toxic factors, such as ergot poisoning,[12] or disturbance of the parathyroid[13] or of the thyroid gland[8] which have in the past been incriminated as causing scleroderma. Raynaud's syndrome appeared after the early skin changes had been established and this can hardly have been the initial cause of the disease as suggested by Brodie.[14]

The symptoms of cardiac involvement appeared about two years before death and after the skin changes were well advanced, but the actual cause of death was congestive heart failure. The associated pulmonary lesions and the interference with thoracic movement by the tight skin of the thoracic wall no doubt contributed to the failure of the already damaged myocardium. There is no clinical or pathologic evidence of any other condition which could account for the myocardial lesions. There was no past history of the common infectious diseases in childhood such as scarlet fever and diphtheria. Rheumatic fever is eliminated both by the clinical and the pathologic findings. In the gross examination of the heart no lesions of the valves were found. There were no typical Aschoff bodies present and the fibrotic areas in this case were not concentrated around the mitral valve ring or in the subendocardial tissues of the left atria.

Acute and subacute endocarditis are discarded as etiologic factors because of the clinical picture and the absence of vegetations on the heart valves. The myocardial lesions showed no evidence of acute inflammatory exudate. Pyemia is also eliminated by the absence of a primary site or of metastatic lesions and by the negative post-mortem heart blood culture and the appearance of the fibrotic lesions. The blood Wassermann and blood Kahn reactions were always negative and there was no evidence of aortitis. The lesions did not resemble those ascribed to syphilis; in fact the existence of syphilitic myocarditis is questioned by many pathologists.[15]

The coronary arteries were patent down to and including their smallest ramifications. Hypertension is eliminated both by the clinical picture and the absence of definite hypertrophy of the heart. Helminthic, protozoal, and viral agents were not found. There was no history of administration of any of the sulfonamides, so that the lesions in the myocardium could not be ascribed to sulfonamide sensitivity.[16] Serum sickness, uremia, poisoning with various chemicals, burns, all of which have been known to cause variable lesions in the myocardium, are manifestly not concerned in the present case. No pathologic lesions suggestive of tuberculosis were found. Disseminated lupus erythematosus may involve the heart muscle but the typical skin lesions and other systemic features were not present. The lesions in the heart did not resemble those ascribed to this condition. Diffuse isolated myocarditis must be discarded as a diagnosis in this case because of the presence of the typical skin lesions of scleroderma. Diffuse myocarditis on the basis of a vitamin deficiency[17,18] is not likely because of the past history of an adequate diet. It seems logical to conclude, therefore, that the damage to the cardiovascular system and lungs was part of the diffuse scleroderma.

The pathologic findings in the skin in this case are characteristic of those described in the textbooks.[19] They can best be interpreted as dependent on a change in collagenous connective tissue. The existing collagenous fibers in the corium become thickened and new ones are formed. In the earlier stages this collagenous tissue is infiltrated in some areas with moderate numbers of lymphocytes and monocytes. The inflammatory cells diminish in quantity as the lesions develop and the collagenous tissue changes become predominant. The collagenous tissue in some areas appears to have undergone fibrinoid degeneration as shown by Masson's trichrome staining method.

The fibrosis of the lungs found in this case has been described by others.[7] Whether it is specific for scleroderma is open to question. Similar lesions are found in cases of organizing pneumonia and in chronic passive congestion. They do, however, resemble the picture of generalized scleroderma and could be explained by an increase of the collagenous tissue in the lung parenchyma. The kidney lesions were not so marked as those described by others.[10] The gastrointestinal tract was free from the lesions lately described by Bevans.[5]

The lesions in the heart are almost identical with those described by Weiss and co-workers[7] and gave rise to definite clinical signs and symptoms. Here again the primary lesion appears to be an overgrowth of collagenous fibers in focal areas throughout the myocardium which extend to the endocardium and pericardium in some areas. These fibrotic areas encroach upon and damage or completely destroy the adjacent myocardial fibers. The fibrosis does not appear to be on the basis of impaired myocardial circulation because, as already mentioned, many patent arterioles were found scattered throughout these areas, and no obstruction was found in the coronary circulatory system.

Clinically and pathologically, it appears that all changes in function and structure observed in this case must be attributed to the diffuse disturbance of collagenous connective tissue which is characteristic of scleroderma.

SUMMARY

1. A case of diffuse scleroderma with characteristic and specific involvement of the heart has been described.

2. Other conditions causing myocardial lesions have been excluded.

3. The specific pathologic changes in the collagenous tissues have been described.

4. Relation to menses, low ketosteroid output, and favorable response to methyltestosterone suggest endocrine disturbance as a possible etiologic factor in this case.

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MULTIPLE LIVER ABSCESSES WITH RUPTURE INTO THE PERICARDIUM

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THE infrequence of sudden rupture of a liver abscess into the pericardial cavity is apparent from the few cases reported in the literature. Huard and Meyer-May[4] observed this complication three times in 150 cases of liver abscess. Ochsner and DeBakey[7] found one example in 181 liver abscesses (amebic). Vergoz and Hermanjot-Gerin,[10] however, found this condition in thirteen of eighty patients with amebic liver abscess. This complication is most likely to occur, for obvious reasons, in those patients not operated on. The mortality rate for liver abscesses with their complications is reported by Ochsner, DeBakey, and Murray[8] to be 79.6 per cent (432 cases). This was in a series of collected cases, whereas in a series of 102 patients not operated upon, the mortality was 100 per cent; on the other hand, in a series of 151 cases in which operation was performed, Ochsner, DeBakey, and Murray[8] report a mortality of 50.9 per cent. It is interesting that the origin of multiple liver abscesses is in the appendix in only about 13 per cent of all patients[6,9]; the abscesses are cryptogenic in about 59 per cent of the patients.[8]

CASE REPORT

An 18-year-old soldier, American-born but of Italian descent, was admitted to a regional hospital Nov. 10, 1945, and died Jan. 10, 1946. His illness began during the first week of September, 1945, while at another camp. His chief complaint was "pain in the stomach." The story was one of rather sudden epigastric pain, sharp in character, and constant though not excruciating. He awakened with the pain on the morning of September 7 and it continued all day. He had eaten a little food but noticed no exaggeration of the pain afterward. He had been on sick call four times in the first three weeks and had been given some liquid medicine and sent back to duty. The bowels had been regular. There was no nausea or vomiting. He stated that he "had fever" off and on during this period. The pains persisted and he continued to stress the upper abdomen rather than the lower abdomen. The localization, as far as one could tell, was in the epigastrium. There was no headache, upper respiratory infection, constipation, or diarrhea accompanying the onset, nor were there any chills recorded then or later, except following two of the blood transfusions (Type O, weak Rh positive).

First Hospitalization.—On admission Sept. 29, 1945, the temperature was 101°F.; the pulse rate, 76; and the respirations, 20 per minute. The patient was noted to have a flaky macular eruption on the shoulders, upper arms, and back; this rash had not been noticed until admission and disappeared after a few days. In addition, there was tenderness bilaterally in the costovertebral angles. During the course of illness he developed an enlarged liver which extended from

From the ASF Regional Hospital, Fort Jackson, S. C.
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two to four fingerbreadths below the right costal margin. These were the only physical findings at the time. Despite chemotherapy consisting of sulfathiazole, sulfadiazine, and 2,000,000 units of penicillin, the temperature continued to reach 103 to 104° Fahrenheit.

In the initial count, the white blood cells were 22,950 with 75 per cent neutrophiles and 8 per cent stabs. The urine showed albumin 2 plus, pus, red blood cells, and a few granular casts. The nonprotein nitrogen of the blood was 58.3 mg. per cent. During his stay in the hospital he ran a persistent leucocytosis. Anemia (2,950,000 red cells; hemoglobin, 9.6 Gm.) developed rapidly. Several cultures of catheterized urine specimens were negative, but on September 30 a culture showed hemolytic *Staphylococcus aureus* and *Staphylococcus albus*, coagulase negative.[2] Many stool cultures were negative except during one brief period of diarrhea which lasted one day (October 16) and was not related apparently to the epigastric pain, when a Shigella, Boyd 88 was cultured. Numerous blood cultures were negative. Liver function tests revealed the following: the cephalin flocculation test was 4 plus and there was an increased prothrombin time (patient, 22 seconds; control, 15 seconds, 68 per cent of normal). Total proteins were 7.5 per cent; albumin, 2 per cent; globulin, 5.5 per cent. The albumin-globulin ratio was 0.36 on October 13. One month after admission, the nonprotein nitrogen was 38 mg. per 100 c.c.; all agglutinations, including the Weil-Felix, as well as the complement fixation for murine typhus, were negative. An intravenous pyelogram showed normal contour and normal mobility of both kidneys. X-ray films of the chest were negative. The only abnormality on a film of the abdomen (October 22) was an enlarged liver.

Second Hospitalization.—On Nov. 10, 1945, the patient was transferred to a regional hospital at Fort Jackson for further treatment. He was admitted with a diagnosis of fever of undetermined origin. His only complaint was epigastric pain. He appeared extremely ill. His complexion was pale and sallow. His face was drawn and anxious, and the eyes were dull. His appetite was poor and constipation was present.

The patient was 5 feet, 2 inches tall and weighed 97 pounds (normal weight, 130 pounds). The temperature was 100.6°F.; the pulse, 100; and the respirations, 24 per minute. He was of small stature, the skin was warm and moist, and his nutrition was poor. The sclerae were clear; neither icterus nor petechiae were present.

One examiner thought there was limitation of movement of the right dome of the diaphragm, but otherwise the chest examination was considered to be negative. Fist percussion in the right lateral and posterior areas of the lower chest did not elicit any unusual response.

The heart size was within normal limits; the sounds were normal; no murmurs were heard. The heart rate was 100 per minute. Blood pressure was 100/85.

The liver was enlarged one fingerbreadth below the costal margin and was slightly tender to pressure. Most of the tenderness was in the epigastrium slightly to the left of the midline, no mass was felt here. Rectal and prostatic examinations were normal.

There was no edema and the deep reflexes were normal. The peripheral vessels were palpable and normal. Pulsations were present in the dorsalis pedis and posterior tibial vessels.

There were 19,900 white blood cells with 72 per cent neutrophiles, 8 per cent stabs, 19 per cent lymphocytes, and 1 per cent eosinophiles. The red blood cells numbered 3,480,000 and the hemoglobin was 11 grams. Repeated urinalyses showed albumin 1 plus to 4 plus, red blood cells, white blood cells, and granular and hyaline casts. Blood cultures during November were still negative. On November 10 the prothrombin time was 80 per cent of normal. The nonprotein nitrogen was now 27 mg. per cent. A brucellergen skin test was negative. All agglutinations were negative. The total proteins were 8.1 per cent: albumin, 3 per cent; globulin, 5.1 per cent. The cephalin flocculation test was 4 plus. The sedimentation rate was 32 mm. in one hour (Wintrobe). A Fishberg[3] concentration test shortly after admission showed a specific gravity of 1.011 (this later improved under therapy to 1.022). A test for urinobilinogen was positive in a dilution of 1:20 but negative in a dilution of 1:40. The Van den Bergh test, both direct and indirect, was negative; the icterus index was 8. The Kahn test was negative. Stool examinations were persistently negative for pathogens. On December 4 a flat plate of the abdomen was negative.

Fluoroscopically, the diaphragm was normal in position and appeared to move freely. On December 14 fluroscopic and radiographic examination of the lungs and heart were negative. Electrocardiogram made on November 23 was normal (Fig. 1).

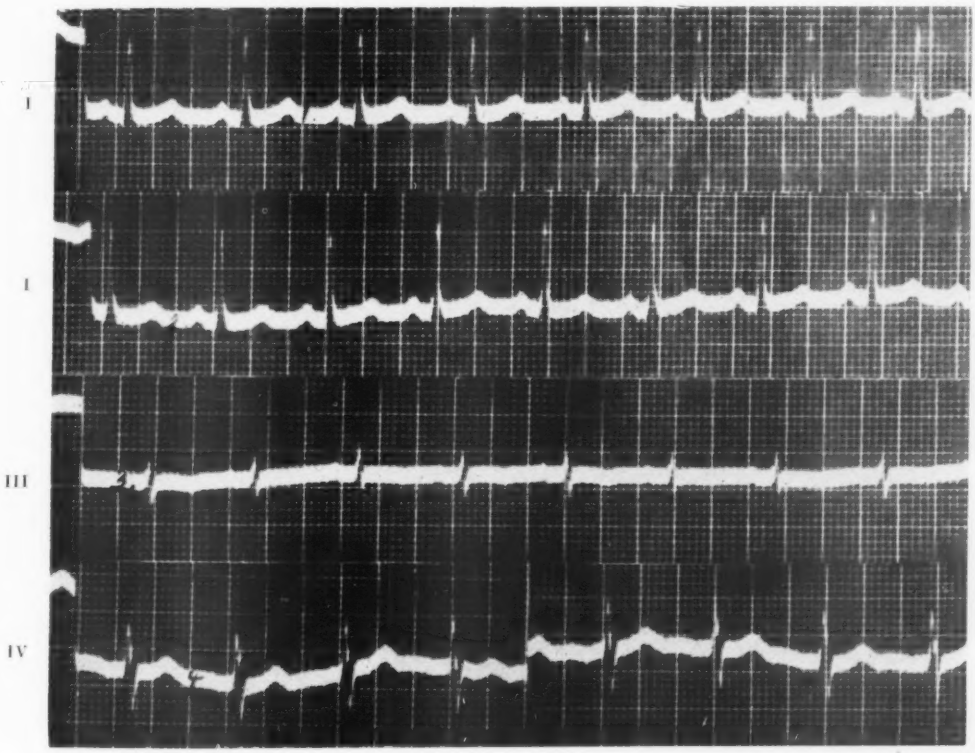

Fig. 1.—Nov. 23, 1945. Rate, 100; normal record.

Because of his poor physical condition, the patient was given repeated blood transfusions for a period of eight weeks. During this period he also received 19,050,000 units of penicillin at three-hour intervals, the dose being 30,000 units at first and 80,000 units later. This produced no effect on the temperature curve, except during the last week of penicillin therapy, when the maximum temperature was 99.6° Fahrenheit. In all other ways, however, he appeared much better: he was more alert and contented, his appetite improved, and there was a gain of four pounds in weight over a four-week period. The erythrocyte count reached a high of 4,250,000, although the leucocytes continued to average 19,000 with 82 per cent polymorpho nuclear cells. By Jan. 2, 1946, he felt so well that he requested discontinuance of the penicillin; with some reluctance this request was complied with inasmuch as the continuous injections over a period of eight weeks, day and night, were a hardship. He was cheerful and began walking about the ward. On January 4, at noon, he left the ward without permission and participated in a lively ball game on the lawn nearby. On January 6, shortly after noon, while playing cards, he suddenly developed severe substernal pain which radiated to the back and to the anterior part of the neck. An x-ray film of the chest made shortly after onsent of this pain was negative (Fig. 5). The pain was severe, steady, and aggravated by breathing and movement of any type. He was in profound shock. There was no nausea or vomiting at first, but vomiting occurred thirty-six hours later. The patient was given morphine and penicillin, 80,000 units every three hours, and placed in an oxygen

tent. He continued to have thoracic pain and discomfort, although this was not as excruciating as at the onset. On January 7 physical examination disclosed an increase in the cardiac dullness to the left as far as the anterior axillary line. On January 8 posteroanterior and right and left anterior oblique films of the chest showed a mild diffuse enlargement of the heart shadow in which the normal contours of the heart were preserved (Fig. 6). There appeared to be small collections of fluid in both costophrenic sulci, slightly greater on the left side. There was also a small amount of vascular engorgement of the pulmonary tree and of the great vessels. Roentgenographic evidence suggested that fluid was present in the pericardial cavity. The white count was now

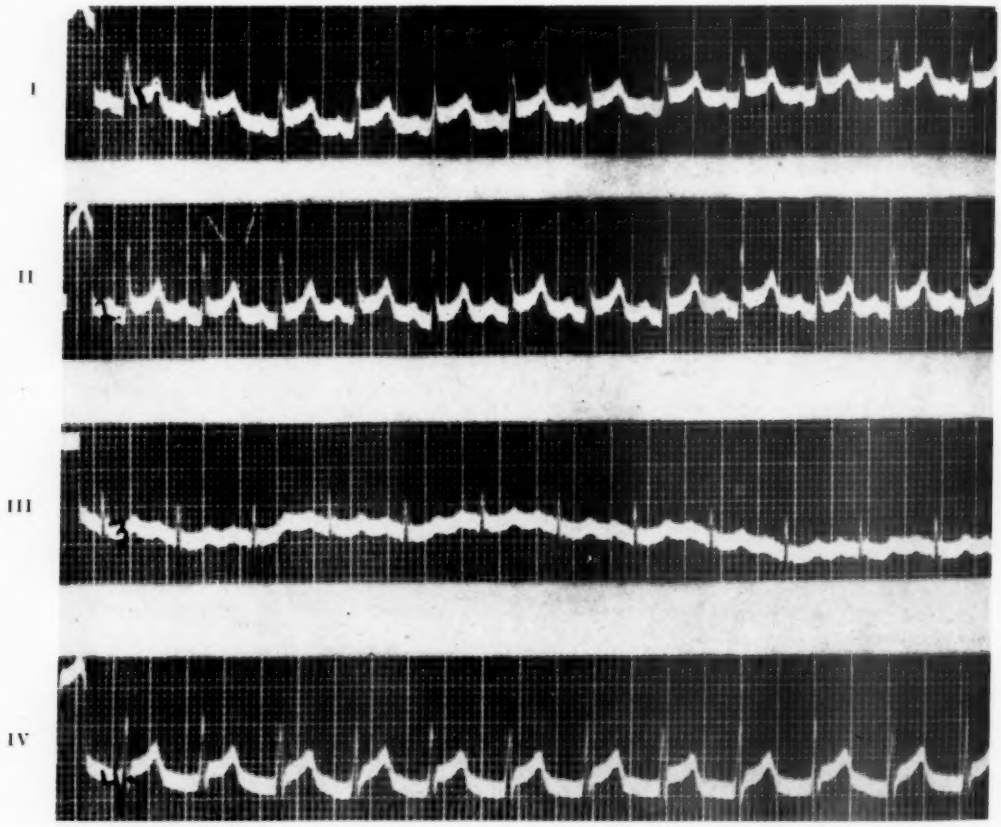

Fig. 2.—Jan. 7, 1946. Twenty hours after rupture. Tachycardia 150; elevated RS-T segments Leads I and II. Findings characteristic of acute pericarditis.

40,000 with 90 per cent polymorphonuclear cells. Posteriorly there were percussion changes and suppression of the breath sounds at the left lung base. A coarse friction rub, synchronous with respirations, was heard in the fifth interspace in the anterior axillary line. The heart rate was accelerated. The sounds were of poor quality and distant. No murmurs were heard. Blood pressure was not obtainable. The radial and brachial arteries could not be felt; pulses parodoxus was not elicited in the carotid arteries. The electrocardiogram now showed changes characteristic of acute pericarditis (Figs. 2, 3, and 4). There was coldness and cyanosis of upper and lower extremities. No pericardial rub was present. The pleural rub had disappeared. The patient ran a progressively downhill course and expired suddenly while his pillow was being changed on Jan. 10, 1946, two days after onset of acute chest episode.

Clinical Diagnosis.—(1) Multiple pyogenic liver abscesses with rupture into the pericardium and left pleural space. (2) Possible hemopericardium, associated with necrotizing arteritis (polyarteritis).

Necropsy Findings.—When the peritoneal cavity was opened, 1,500 c.c. of clear amber-colored fluid was recovered. The peritoneal surfaces were smooth and glistening; the loops of intestines were normally disposed. The omentum hung, apronlike, over the intestinal loop in the upper half of the peritoneal cavity. The loops of the small bowel were distended with gas and

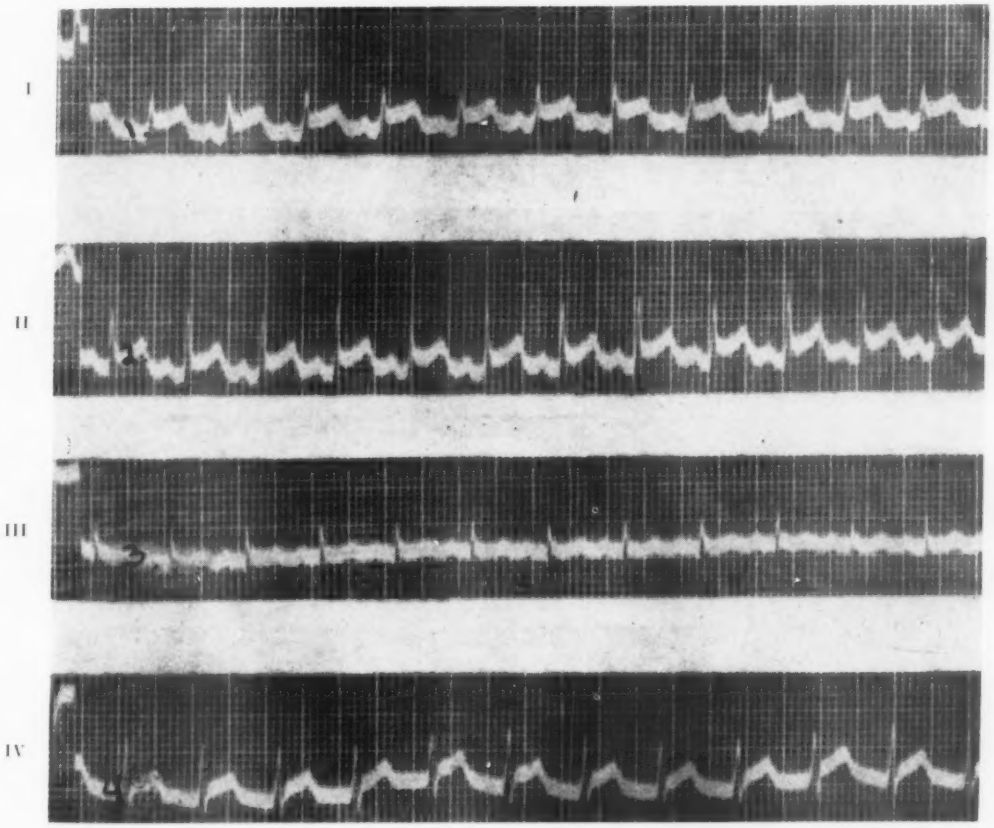

Fig. 3.—Jan. 8, 1946. Forty-eight hours after rupture. Low voltage QRS_1 and QRS_3, elevated RS-T segments in Leads I and II. Findings typical of acute pericarditis.

were hyperemic. Palpation and section of the portal vein radicals revealed nothing other than nonclotted dark red blood. The appendix was present and normal in appearance. The lower edge of the liver extended 5 cm. below the costal cage in the midclavicular line on the right. The diaphragm was adherent to the upper surface of the liver on both sides. The fibrous adhesions were delicate and friable on the right but were dense on the left. The diaphragm extended to the level of the fifth rib on the right and the fourth rib on the left. On opening the pleural cavity, the right lung was found to be partly collapsed and about 300 c.c. of turbid, straw-colored fluid were present. The left lung was collapsed to a similar degree and an estimated 150 c.c. of the same type of fluid were present in the left pleural space.

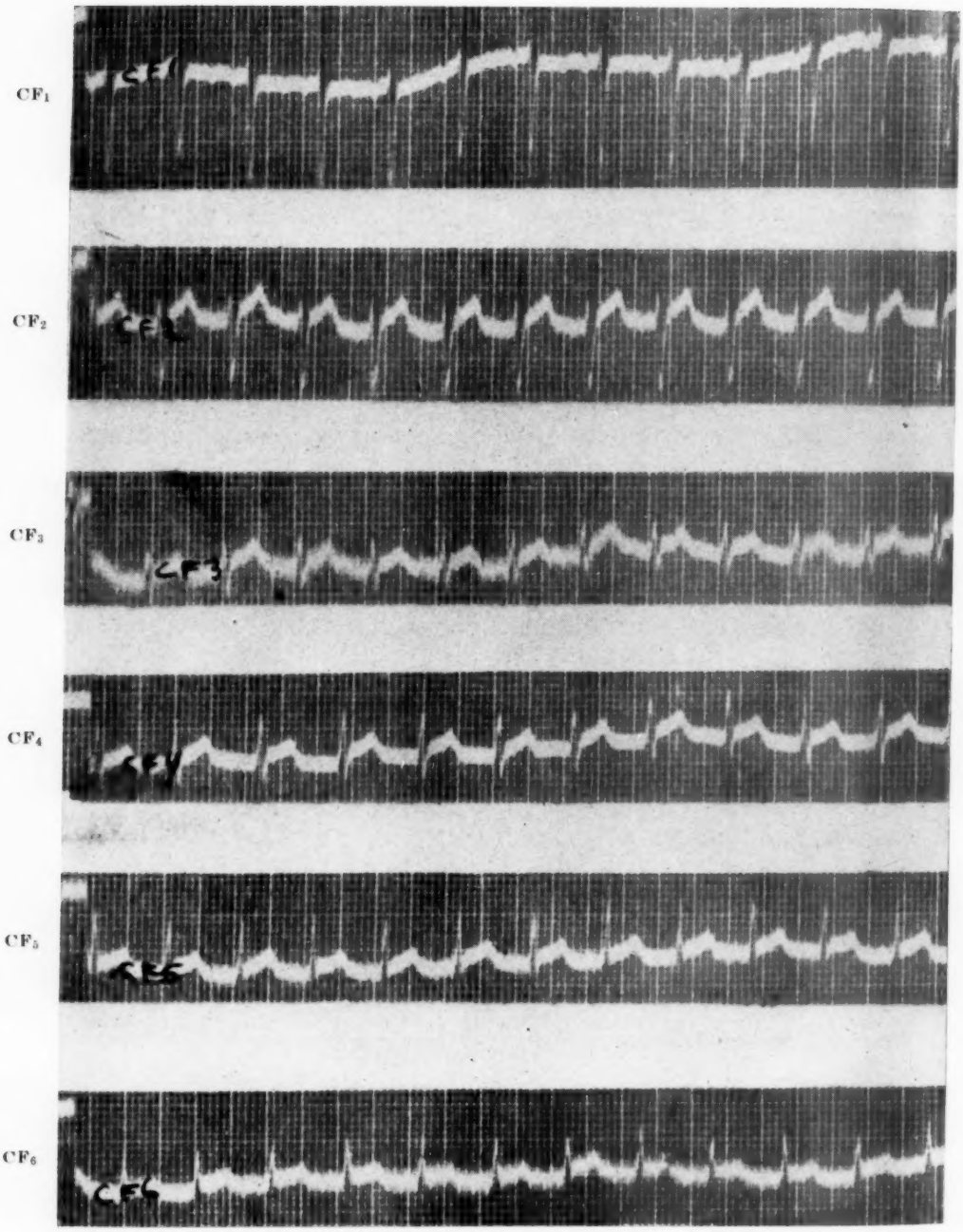

Fig. 4.—Jan. 8, 1946. Chest leads (CF series) taken at same time as limb leads shown in Fig. 3. Essentially normal except for slight depression of S-T segment and flattened T in CF_1.

The pericardial sac was very greatly enlarged and was thickened and fibrous. The walls were tense and translucent. Delicate, fibrous adhesions existed between it and the contiguous pleural surfaces. This sac extended from the level of the sternoclavicular joint to a point in the left chest which was 9 cm. from the midline in the fifth intercostal space. The upper portion of the pericardial sac was 5 cm. in width in the sternoclavicular area and extended 6 cm. to the right of the midline at the level of the second interspace. The pericardium when opened was found to contain 400 c.c. of greenish-yellow turbid fluid. Floating in this fluid were large, ragged, light yellowish-green clumps of fibrinopurulent exudate. The parietal and visceral pericardium were

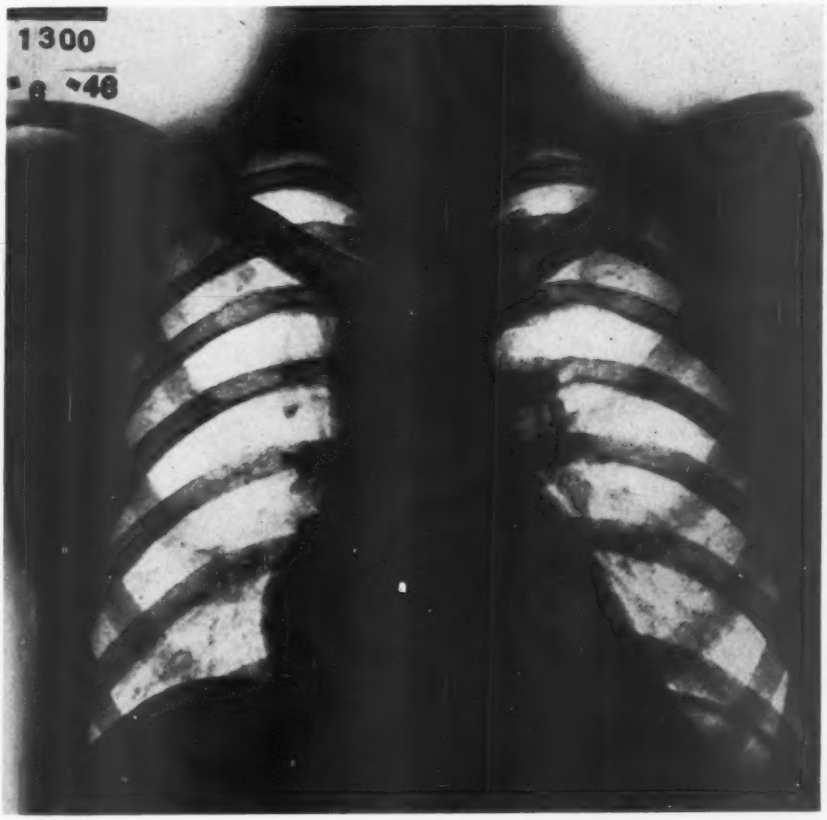

Fig. 5.—On day of rupture, x-ray negative. Size and contour of heart unchanged from previous films.

covered with a shaggy but delicate fibrinous exudate. This exudate covered all surfaces of the heart and great vessels so thickly that underlying epicardium was obscured. No gross perforations were demonstrated in the pericardium. The heart weighed 360 grams. The left ventricular myocardium was 9 mm. thick and that of the right ventricle was 4 mm. thick. The endocardial surfaces were normal as were the valve leaflets. The internal surface of the ascending aorta was light yellow in color and smooth in character. The coronary ostia were of the usual size. The left lung weighed 380 grams and the right 390. The lower lobes of both lungs were dark red. On section the cut surfaces revealed congested dark red lung tissue from which frothy sanguinous fluid exuded on pressure.

The liver weighed 1,980 grams. When the dense fibrous adhesions connecting the uppermost portion of the left lobe and the diaphragm were dissected, there was found a large left subphrenic abscess which involved 65 per cent of the left diaphragmatic area. This abscess cavity contained 175 c.c. of thick, light jade-green pus. Further dissection revealed a tract which led from the subphrenic abscess to a necrotic abscessed area involving the left lobe of the liver. Around this tract the diaphragm was so densely adherent to the surface of the left lobe that dissection could only be accomplished with sharp scissors. The upper surface of the left lobe showed a moderately deep concave deformity caused by the adjacent subphrenic abscess. On

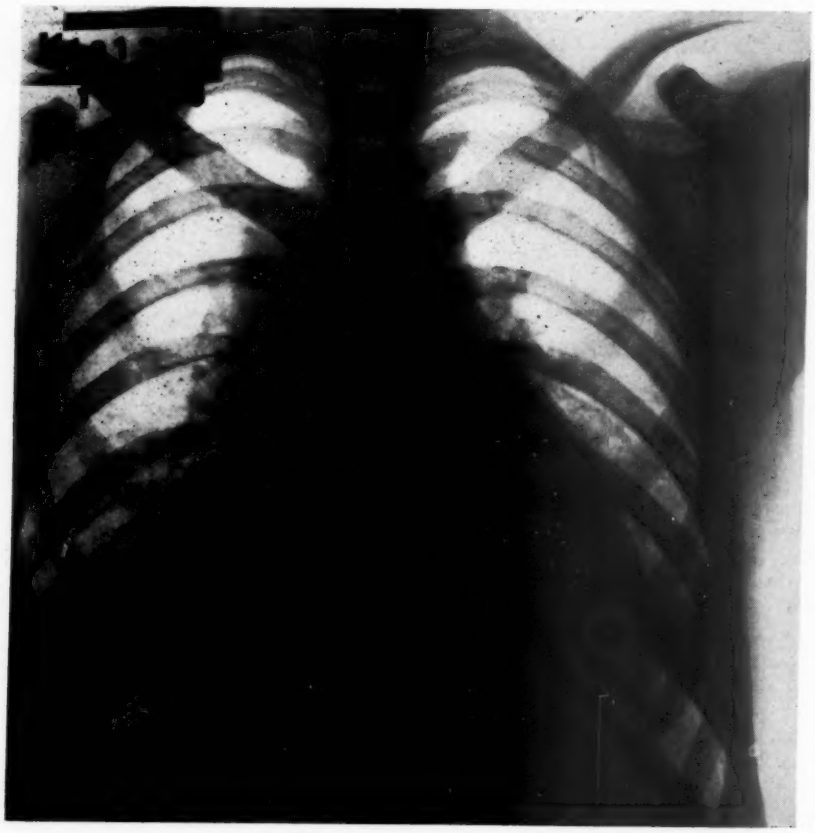

Fig. 6.—Forty-eight hours after rupture. Diffuse enlargement of heart shadow in which normal contours are preserved. Small collection of fluid in left costophrenic sulcus. Widening at base not entirely due to pericardial fluid but to vascular engorgement of pulmonary tree and great vessels.

section, the right lobe presented a nutmeg appearance. Sections further to the left revealed that the upper one-half of the left lobe and a small portion of the adjacent middle lobe contained light yellow-brown necrotic hepatic tissue in which there was cavitation in the area of the tract that communicated with the left subphrenic abscess. In all these cavities the same type of light green, thick, purulent material was present. The gall bladder showed no abnormalities. The gastrointestinal tract showed no gross pathologic change in its entire course. Each kidney weighed 220 grams. There were small subcapsular hemorrhages present over the upper poles of both kidneys. On section the normal renal architecture was present. The cortex and medulla were hyperemic. The adrenals were normal as were the ureters, urinary bladder, prostate, and testicles.

There were no striking changes in the spleen. The pancreas was normal. The brain showed some gross hyperemia and edema of the cortex. No abnormalities of the vascular or neural patterns were observed.

The smear and culture of the abscess fluid revealed *Staph. aureus*, nonhemolytic.

Anatomic Diagnosis.—(1) Acute fibrinopurulent pericarditis. (2) Chronic subphrenic abscess. (3) Chronic passive hyperemia of the lungs. (4) Chronic focal suppurative hepatitis, with multiple abscesses of left lobe of liver.

DISCUSSION

In this particular case it was felt that the liver abscesses were multiple and the patient too poor a risk for surgery. Some may argue, with statistical justification,[8] that surgery should have been attempted. After viewing the autopsy, however, it was felt that drainage would have been inadequate because the numerous abscesses in the left lobe were inaccessible to any surgical approach. On the other hand, Huard and Meyer-May[4] reported a case of solitary abscess of the left lobe of the liver followed by an aseptic puriform pericarditis with recovery after trans-sternoxiphoid drainage; the abscess was located with iodized oil. It was also of interest that about two weeks prior to the sudden rupture of the abscess, we attempted to detect limitation of motion of the diaphragm by fluoroscopy but were unable to see anything but normal movements. The location of the pathology in the left lobe of the liver undoubtedly accounts for this.

The rupture of the abscess into the pericardium followed by four days the cessation of penicillin therapy and by two days the violent exercise on the lawn. The acute episode, when it occurred, looked like an acute vascular accident; coronary thrombosis, hemopericardium, or rupture of a dissecting aneurysm was thought possible. One excellent observer, who had not previously seen the patient, thought of a polyarteritis with necrotic changes in the vessel walls which might have been responsible for the bizarre general symptomotology as well as for a possible sudden pericardial hemorrhage. The electrocardiogram had shown changes characteristic of an acute pericarditis and the latter suggestion seemed reasonable. The possibility of liver abscess rupturing into the pericardium, however, was thought more likely. A pericardial tap was suggested for diagnostic purposes but since evidence of effective tamponade was not present, conservatism prevailed and it was not done.

The electrocardiogram taken twenty hours after onset (Fig. 2) showed typical changes of acute pericarditis mainly in the first two limb leads. Forty-eight hours after onset, the limb leads were unchanged (Fig. 3). The six chest leads (CF series) added little; the only definite finding was an extremely low voltage T wave in CF_1, with slight S-T depression[5] (Fig. 4). The remaining chest leads were within normal limits. The electrocardiograms are of interest in that the changes which they revealed were not seen in any of the very few case reports of this complication of liver abscess.[1,4]

SUMMARY

1. A case of multiple pyogenic liver abscess with complicating sudden rupture into the pericardial sac is presented.

2. The source of the liver abscess was not found at necropsy.

3. Penicillin, 19,050,000 units, plus supportive therapy over an eight-week period, held the infection in abeyance but did not overcome it. The responsible organism was penicillin sensitive as judged by the clinical response.

4. Typical electrocardiographic changes of acute pericarditis were demonstrated in the limb leads, with minimal findings in the chest leads (CF series).

The author wishes to acknowledge the suggestions and comments on this case by the following: Lieutenant Colonel Walter C. Bartlett, Major Griffith Radcliffe, and Major Jacob Silverman, Medical Corps, Army of the United States. The necropsy was performed by Captain Edwin Albright.

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In Memoriam

CARL J. ROTHBERGER

1871-1945

Friends of Professor C. J. Rothberger of Vienna will learn with deep regret that he was killed during the war when his home was hit by an aerial bomb.

With his demise, medicine has lost one of the last great investigators of the classic period of electrocardiography. His identification of the total irregularity of the pulse, the delirium cordis, with auricular fibrillation (in collaboration with Winterberg) met with resistance and was accepted only when Sir Thomas Lewis made the same discovery independently soon afterward. Rothberger described bundle branch block in the experimental animal (with Eppinger) and also in man. A series of fundamental studies on the influence of the tonus of the cardiac nerves on the electrocardiogram, on auriculoventricular rhythm, and on the origin of extrasystoles followed. In collaboration with Kaufmann, parasystole was described and analyzed in a series of papers. The hope that extrasystoles with fixed coupling could be based on a parasystolic mechanism was not fulfilled, but a new and interesting disturbance was discovered. In the later years, the studies on the mechanism of origin of extrasystoles were continued and the importance of the after-potential for the appearance of extrasystoles was investigated (with Goldenberg).

Rothberger had an unusual experimental skill which he improved early in his career in the laboratory of Pavlov. Afflicted with otosclerosis which caused almost complete deafness, he spent his days exclusively in the study of electrocardiographic problems. He had a clear and lucid style, and his reviews, particularly that in Volume 32 of *Ergebnisse der Physiologie*, are milestones in the science of cardiology.

In the years before 1938, physicians from all over the world, among them many from the United States, worked in his laboratory. He was to all an unselfish helper and advisor and with his kindly personality made a host of friends who will be saddened by the news of his death.

With the conquest of Austria in 1938 he lost his position, his library, and the opportunity to work or to publish the results of his studies. Unfortunately, he was not spared to live to see the day of liberation.

DAVID SCHERF
PAUL D. WHITE

CESARE PEZZI

1874-1945

Less than a year ago Europe lost one of its best cardiologists, a great soul, and a modest man. We can say "Europe" because Pezzi, though Italian, was known better in his adopted country, France, than in Italy.

A few years after he obtained his medical degree from the University of Pisa in 1899, Pezzi went to Paris and devoted himself to experimental research, first, in the Laboratory of Richet and later in that of Pachon. Then, attracted by the rising star of Vaquez, he joined him at the Hôpital de la Pitié and became one of his better known pupils.

Although his residence in Paris was meant to be short, it lasted about twenty years. These years were employed in continuous and fruitful work which included graphic studies on the apex beat and jugular pulse tracings, studies on premature beats, sinus arrhythmia, heart sounds, the action of calcium on the vagus nerve, production of auricular fibrillation, action of nicotine, A-V heart block, pulsus alternans, and gallop rhythm. Pezzi also studied congenital heart diseases and gallop rhythm. The vigorous pulsation of the pulmonary vessels, described by him in pulmonic insufficiency, was later called hilar dance or Pezzi's sign. During the first years of this period he was one of the founders of the *Archives des Maladies du Coeur* in which many of his articles were subsequently published.

From 1915 to 1919 Pezzi took part in World War I, fighting with the Italian Army. Some studies on cardiac wounds were accomplished during his war service. At the end of the war he was one of the founders of the Italian periodical *Malattie del Cuore e dei Vasi* whose title was later changed to *Cuore e Circolazione*.

During the period 1919 to 1921, Pezzi worked again in France. Then, having lost his beloved wife, he went back to Italy and, on the advice of his friends, settled in Milan, near his home town. However, although Pezzi lived in Italy after 1921, frequent trips to Paris kept him in contact with the French school, as is proved by his books. One of them, *Roentgenology of the Heart and Vessels* appeared in Milan, but two others were published in France, in collaboration with Laubry. They are: *The Gallop Rhythms* and *The Congenital Diseases of the Heart.*

After his return to Italy, Pezzi tried in vain to obtain official recognition of his work. While recognized as a well-known specialist, he was unable to obtain any important position in the hospitals or in the medical schools. There were several reasons for this: his modesty, his long sojourn in France, and his uncompromising attitude toward Fascism.

The increasing fury of Fascism finally led to political persecution, so that Pezzi was obliged to lead a secluded life during World War II. For some time his friend Laubry was able to correspond with him at rare intervals; then news ceased completely.

The name of Pezzi should be preserved in the minds of all cardiologists, not only because of his work, but also because of his integrity and honesty which have been recognized by friends and enemies alike.

A. LUISADA

Abstracts and Reviews

Selected Abstracts

Ramos, J. G., and Peralta, B.: Action of Digitalis and Ouabain on Certain Properties of the Myocardium. Arch. Inst. cardiol. México **16**:93, 1946.

The effects of various concentrations of digitoxin and ouabain on certain cardiac functions were studied by simultaneous electrical and mechanical recording. The heart rate, amplitude of isotonic contraction with different loads and different initial tensions, velocity of transmission of the impulse, and capacity to perform work were studied in isolated and perfused amphibian hearts. The velocity of transmission of the impulse and blood pressure changes were studied in cats under dial anesthesia.

These experiments revealed no consistent or clear-cut difference in the action of the two drugs. The authors suggest that the pharmacodynamic and clinical difference between them is due to one or more of the following factors: (a) different action on the autonomic nervous system, (b) different action on blood vessels, (c) different route of administration, (d) different degree of fixation by the tissues, (e) different rate of destruction or excretion.

Effective concentrations of both drugs shortened the P-R interval and increased the capacity for work but caused no change in the heart rate. Toxic concentrations of both drugs, on the other hand, slowed the heart rate and prolonged both the P-R and Q-S intervals, in addition to producing other well-known changes.

The authors attribute the increased capacity for work produced by these drugs to three factors: improved synchronization of the fibers during contraction, prolongation of the contraction, and decrease in the viscosity of the muscles. Toxic concentration of the drugs was found to increase the viscosity of the cardiac muscles. LUISADA.

De Vries, A.: Changes in Hemoglobin and Total Plasma Protein After Injection of Mercurophylline. Arch. Int. Med. **78**:181 (Aug.), 1946.

Various studies of the mercurial diuretics have indicated that their site of action is the kidney and that they produce diuresis by diminishing tubular reabsorption. Evidence that diuresis is the result of an extrarenal action is less convincing. The author considers that a primary extrarenal action of these drugs, which brings about a transfer of tissue fluids to the blood stream, would result in a temporary hydremia; that is, an increase in the plasma volume with a fall in hemoglobin and plasma protein. A preponderantly or exclusively renal action, on the other hand, would cause hemoconcentration. Fluctuations of hemoglobin and total plasma protein were therefore studied in 34 patients during the diuresis following injection of mercurophylline.

In patients who had edema, the average change in hemoglobin and in total plasma protein observed seven to twenty-eight hours after the injection of mercurophylline did not differ significantly from zero in statistical analysis. In patients in whom there was no edema, there was a significant rise in hemoglobin and in total plasma protein seven to twenty-eight hours after injection. In this group, the rise in hemoglobin and total plasma protein was higher with an increasing rate of diuresis. In the patients with edema, the changes in hemoglobin and total plasma protein were not dependent on the rate of diuresis.

These results indicate that a diuresis produced by mercurophylline causes hemoconcentration which, in the presence of peripheral edema, is compensated by a rapid inflow of interstitial fluid into the blood stream. This interpretation is consistent with the theory of the renal action of mercurial diuretics. BELLET.

Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel: II. Effectiveness of Intensive Salicylate Therapy in Cases of Acute Infection. Arch. Int. Med. **78**:170 (Aug.), 1946.

Studies of salicylate therapy were made in a series of seventy-seven young men with acute rheumatic fever, all of whom exhibited acute polyarticular arthritis as a major manifestation. Fifty-four patients received intensive salicylate therapy patterned after the regimen outlined by Coburn. Of this group, thirty-five received intravenously 10 Gm. of sodium salicylate in 1 liter of lactate Ringer's solution or isotonic sodium chloride solution daily for four to ten days; this was followed by oral therapy. The remaining nineteen patients received only oral therapy throughout the course of treatment. The twenty-three patients who comprised the control group received small quantities of salicylate for symptomatic relief of acute symptoms.

The results obtained in the intensively treated and the control groups were compared on the basis of temperature, articular manifestations, erythrocyte sedimentation rate, electrocardiographic and clinical findings, and the incidence of relapse and residuae. In the fifty-four patients who received intensive therapy, the average duration of fever was 36 days, and of objective articular manifestations, 2.8 days. In striking contrast, the average duration of fever in the control group was fifteen days and of objective articular manifestations, twenty-six days. The average duration of elevated erythrocyte sedimentation rate was twenty days in the intensively treated patients and forty-two days in the control group. The cardiac manifestations at the termination of treatment were carefully studied. Of the patients who received intensive therapy, 71 per cent showed no evidence of residual cardiac damage; 15 per cent were classified as having potential rheumatic heart disease on the basis of a slight or moderate mitral systolic murmur. Seven and four-tenths per cent of the intensively treated group had significant carditis when treatment was instituted. This process cleared up completely in all but one patient who was left with a moderate mitral systolic murmur. Significant cardiac residuae were present in 7.4 per cent of the group receiving intensive therapy; only one patient died of heart disease. Significant carditis did not develop in any patient who had not shown evidence of carditis before treatment was begun. In the control group, on the other hand, only 48 per cent of the patients escaped with undamaged hearts, 39 per cent were classified as having potential rheumatic heart disease, and 4.3 per cent had significant carditis which cleared up. In 13 per cent, significant cardiac residua were present. The incidence of chronic infection, as determined by residual arthritis and increased sedimentation rate, was 6 per cent in the intensively treated group and 18 per cent in the control group.

The author concludes that the period of active infection is materially shortened and that relapses and residual chronic infection, although not prevented, occur less frequently in patients receiving intensive salicylate therapy than in those who receive symptomatic therapy. Except in occasional severe and refractory infections, salicylate administered orally is as effective as salicylate administered intravenously. Carditis present prior to treatment was favorably influenced by intensive salicylate therapy; resulting cardiac manifestations were distinctly less in the intensively treated as compared with the control group. BELLET.

Bridges, W. C., Johnson, A. L., Smithwick, R. H., and White, P. D.: Electrocardiography in Hypertension: Study of Patients Subjected to Lumbodorsal Splanchnicectomy. J. A. M. A. **131**:1476 (Aug. 31), 1946.

The authors describe the changes in the electrocardiogram which are frequently encountered in patients with diastolic hypertension after the reduction of blood pressure by lumbodorsal sympathectomy. A comparison was made between the preoperative and postoperative electrocardiograms taken two weeks and one year or longer after sympathectomy in the cases of 144 patients who were observed for at least one year. Preoperatively, these cases were divided into

three groups on the basis of pulse pressure in relation to the diastolic level. Type I comprised patients with the narrowest and Type III those with the widest pulse pressures. The following electrocardiographic changes were noted:

In the limb leads, 44.5 per cent of the preoperative records were abnormal or borderline. There was a progressive improvement in the abnormal records following operation. Sixty-seven per cent of the total series were normal two weeks postoperatively, and 78.5 per cent were normal at the end of a year. The most favorable group for operation, Type I, had the highest percentage of normal preoperative records. The greatest return to normal occurred in the most unfavorable group, Type III. Following operation, a swing of the electrical axis of more than 10 degrees toward the right took place in 34.1 per cent of the cases by the end of a year. R_1 decreased in amplitude more than 3 mm. in 41.7 per cent of the cases after one year. The T waves preoperatively were abnormal in 25 per cent of the cases. A year after operation the T waves were practically normal in Lead I in 86.1 per cent of the cases and in Lead II in 90.9 per cent.

In the chest leads, 50 per cent were abnormal preoperatively. There was a return to normal by the end of one year in 15 per cent. The T waves of the chest leads when abnormal, tended to improve in each lead postoperatively.

From this study, the authors conclude that when hypertensive patients with electrocardiographic evidence of cardiac strain, which is often the first manifestation of impending or actual heart disease, are subjected to bilateral lumbodorsal sympathectomy, they frequently show an improvement in the hypertensive electrocardiographic pattern one year or more postoperatively. This is consistent with the decreased work of the left ventricle. BELLET.

Perrin, P.: Consideration of the Pathogenesis and Treatment of Functional Cardiac Symptoms in 50 Year Old Men. Arch. J. mal. du coeur **39**:96 (March-April), 1946.

Symptoms of dyspnoea and tachycardia on effort, often accompanied by chest pain, are frequent in men about 50 years of age who have no objective evidence of heart disease. This type of illness is often very refractory to treatment. The author reports, however, that he obtained striking symptomatic improvement by the injection of vitamin B, 1 mg. every second day, and of testosterone, 25 mg. twice a week. The selection of medication was based on the views of Jayet-Lavergne that vitamin B has a specific effect on cellular polarization in the male. It is emphasized that although the explanation of the mode of action of the treatment is admittedly speculative, the clinical results have been most encouraging in a large group of patients who had received little or no benefit from other forms of therapy. LAPLACE.

Leblanc, M.: Micro-Nodulation, a Manifestation of Pulmonary Stasis in the Presence of Mitral Disease. Arch. J. mal. du coeur **39**:69 (March-April), 1946.

A case of mitral stenosis is reported in which x-ray examination revealed dense mottling throughout both lung fields due to the presence of miliary nodules and what appeared to be small cavities. This condition is easily confused with tuberculosis. Actually it is a rare manifestation of pulmonary stasis due to mitral disease. It is persistent and is not altered by clinical improvement in heart function. It has been ascribed to accumulation of carbon or hemoglobin due to stasis and intra-alveolar edema. LAPLACE.

Lian, C., and Guinard, P.: The Practical Importance of Auscultation in the First Right Intercostal Space. Arch. J. mal. du coeur **39**:92 (March-April), 1946.

The authors believe that the importance of auscultation in the first right intercostal space should be better appreciated. Systolic murmurs which arise from the aorta are almost invariably loudest in this area. There are two circumstances in which this fact may be helpful in diagnosis. When a patient is suspected of having mitral insufficiency and the systolic murmur extends to the base of the heart, if the murmur is best heard in the first right interspace, it is aortic in origin, irrespective of the presence or absence of mitral disease. When a systolic murmur is of equal intensity in the second right and left interspaces, it is aortic and not pulmonic if it is loudest in the first right interspace. Occasionally this area may also be the only site at which an aortic diastolic murmur can be heard. LAPLACE.

Galli, F.: Considerations on a Rare Case of Dextrocardia (Isolated Dextrocardia With Inversion of the Chambers). Cuore e circolaz. **30**:13 (No. 12), 1946.

The published cases of dextrocardia are reviewed and it is noted that when this congenital anomaly is isolated and not associated with inversion of other viscera, the cardiac chambers are usually in a position similar to that of a normal heart, but displaced to the right. A case is reported in which there was an isolated dextrocardia but the chambers were a mirror image of the normal. It is, therefore, the sixth published case of this rare anomaly.

The patient was an 18-year-old girl who complained of exertional dyspnea and palpitation. The heart was centrally placed, and there was an "apical" systolic murmur over the right side of the heart, transmitted to both the right axilla and the fourth left interspace. The spleen and liver were in normal position. A chest film revealed a "mirror-like" image of the heart, with the esophagus at the right of the spine but the stomach in the normal position. The general shape of the heart was rounded; the retrocardiac space was reduced. The right (actually the left) auricle was somewhat enlarged. The electrocardiogram showed a typical mirror-image appearance in Lead I; Lead II showed an inverted T wave.

The author attributes the electrocardiographic changes to inversion in the position of the conduction system in relation to the electrodes. The final diagnosis was dextrocardia with mitral valve defect. LUISADA.

Kramer, Milton L., and Kahn, J. W.: The Effect of Atropine on the Branham Sign in Arteriovenous Fistula. Arch. Int. Med. **78**:28 (July), 1946.

The phenomena of the Branham sign, which consists of the slowing of the pulse rate upon temporary obliteration of the arteriovenous fistula, suggests that it is due to a reflex arc in which the vagus nerve is the efferent pathway. Although patients with the larger fistulas show the most striking changes in pulse rate, the Branham phenomenon is also observed in patients with small fistulas.

The authors studied the effects of atropine on the elimination of the Branham phenomenon in patients with arteriovenous fistula. The heart rate, pupillary changes, and dryness of the mouth were utilized as evidence of atropinization. In nine of the ten cases thus studied, there was considerable fall in the pulse rate on obliteration of the fistula prior to atropinization, but the slowing failed to appear following administration of atropine. The changes in the blood pressure usually associated with obliteration of the fistula, namely, rise in diastolic pressure and reduction of pulse pressure, were not influenced by atropine. BELLET.

Chenoweth, M. B.: The Cardiovascular Actions of 2,3-dimercaptopopanol (BAL). J. Pharmacol. & Exper. Therap. **87**:41 (Aug.), 1946.

BAL exerts its most important systemic actions on the central nervous and cardiovascular systems. Because of the presence of a pronounced circulatory effect, a detailed investigation of its action was made. BAL administered to cats intravenously resulted in a fall of the systemic and pulmonary arterial and venous pressures and in a rise of the portal pressure. When administered in very small repeated intravenous doses or by pericutaneous application, BAL caused a rise in blood pressure. There was a marked rise in the peripheral resistance of the limb vessels during the period of falling blood pressure but none in the vessels of the liver or splanchnic areas.

Electrocardiograms (Lead II) were obtained in three anesthetized cats. Changes in heart rate were slight. Decrease in the voltage of the R wave, deepening of the S wave, elevation of the S-T segment, occasional ectopic beats, brief periods of ventricular tachycardia, and lowering of the T wave were observed at different times in the three cats.

Following the administration of BAL, the hematocrit reading was increased, while at the same time the concentration of injected dye in the blood was reduced. This paradoxical result is probably due to the loss of the dye from the blood stream. Blood volume, calculated on the basis of the hematocrit readings, was found to decrease by 30 per cent, whereas in the calculations

based upon the change in the dye concentration, the blood volume was found to increase by 27 per cent.

Administration of BAL resulted in a marked increase in the rate of lymph flow from the thoracic and cervical ducts.

The experimental data presented in this report supports the view that the major action of BAL on the cardiovascular system is twofold: a marked increase in capillary permeability as a result of the action of the drug on the walls of these structures; and a peripheral arteriolar constriction resulting from a direct action of BAL on the arteriolar structures. A third action, which is negative in character, is the absence of vasoconstriction of the splanchnic arterioles. The various changes in the circulatory system are probably secondary to these three phenomena. BAL presents a very interesting phenomenon from the pharmodynamic point of view. The action of potent vasoconstricting agents is customarily regarded as being general throughout the vascular bed. The reaction to BAL is decidedly atypical in that peripheral arterioles are markedly constricted while splanchnic arterioles are unaffected. The action of BAL on the peripheral arterioles has been shown to be on the arteriolar structure, and it may be assumed that the sensitive component of the peripheral vessels is absent from the splanchnic bed. BELLET.

Ross, I. S.: Cerebral Vascular Occlusions in Young Adults. J. Nerv. & Ment. Dis. **104**:51 (July), 1946.

The author reports a series of six cases of young adults who suddenly experienced a destructive cerebral lesion unaccompanied by subarachnoid bleeding and followed by permanent residual sequelae. These patients were free from syphilis, hypertension, atherosclerosis, bacterial endocarditis, and blood dyscrasias. In the absence of a final pathologic examination, no conclusion could be made as to the type of lesion which was present. The author believes, however, that the anatomical-pathological disorder common to these cases was a localized atherosclerosis such as has been found repeatedly in occlusion of coronary arteries in relatively young people. Death is unusual from a single cerebral infarction in this age group. BELLET.

Castro, V. Alzamora: The Influence of a Nonindifferent Electrode Upon the Precordial Electrocardiogram. Gac. med. de Lima **2**:181 (Jan.), 1946.

The distorting influence of the potential variations of the extremities upon the precordial electrocardiogram in Leads C_L, C_F, and C_R is clearly demonstrated and the distortion is predicted by the use of unipolar limb leads. Although the alterations induced by the "indifferent" electrode when placed on one of the extremities are rarely excessive, the advantages of using a central terminal is emphasized on practical and theoretical grounds. HECHT.

De La Barreda, P., and Jimenez-Diaz, C.: The Action of Urinary Extracts of Normal and Hypertensive Individuals and of Hypertensive Dogs Upon the Arterial Pressure. Rev. clin. españ. **205**:25 (Jan. 15), 1946.

Alcoholic extracts of urines from hypertensive patients and from dogs made hypertensive by cellophane perinephritis failed to cause an elevation of blood pressure in anaesthetized normal and hypertensive dogs and in rabbits. Some of the extracts showed hypotensive effects; others seemed to block and reverse the rise in pressure following epinephrine and alloxan. HECHT.

Cossio, P., and Sotomayor, O.: Paroxysmal Tachycardia With Syncope. Prensa med. argent. **33**:903 (May 3), 1946.

Four cases are presented in which syncope occurred with the onset of attacks of paroxysmal tachycardia. In three patients the paroxysms arose from a ventricular focus and in one, from a supraventricular focus. The differential diagnosis of syncope in general is discussed and five types are listed: traumatic syncope (head or abdominal injuries), reflex syncope (carotid sinus syndrome), blood-loss syncope, orthostatic syncope, and cardiac syncope. The latter is further

subdivided into syncope following the onset of ventricular fibrillation, syncope occurring during a sudden onset of auriculoventricular block with failure of idioventricular rhythms to develop, syncope with cardiac tamponade, syncope "on effort" (Gallavardin), and syncope associated with paroxysmal tachycardia. The importance of an accurate diagnosis is again emphasized, for the treatment for one type may be contraindicated for others. Since syncope due to paroxysmal tachycardia is an infrequent event, the previous state of the heart muscle and the peripheral vascular system must be important contributory factors. The incidence of syncope is higher in ventricular tachycardias than in those of the supraventricular type because instances of the former are more commonly associated with cardiovascular disease. HECHT.

Parra, J., and Franco, R.: Myocardial Changes Following Sulfonamides. Rev. clin. españ. **20**:331 (Feb. 28), 1946.

A 69-year-old woman received approximately 50 Gm. of a sulfonamide over a period of ten days for an anthrax infection of the neck. Twelve days later pneumonia occurred and a second course of sulfonamide was prescribed, 7 Gm. daily for six days. The patient recovered but returned one month later with signs and symptoms of congestive heart failure. Treatment was unsuccessful and the patient died. At autopsy a few scars were found in the left ventricle, and a histological examination revealed what is merely described as "intense muscular degeneration and fatty infiltration." The absence of previous heart disease led the authors to assume that the myocardial changes were brought about by the excessive administration of sulfonamides.

HECHT

Silbert, S.: Medical Management of Peripheral Vascular Disorders. Bull. New York Acad. Med. **22**:397 (Aug.), 1946.

The author reviews the present-day treatment of arterial embolism, thrombophlebitis, arteriosclerotic disease of the extremities, and thromboangiitis obliterans and discusses briefly some important considerations in regard to treatment of these four conditions. In regard to embolism, he stresses the importance of elevating the head of the bed, the application of cold instead of heat, the use of vasodilator methods such as intravenous papaverine, one grain every two hours for four doses, and the use of continuous sacral anesthesia. In thrombophlebitis prophylactic measures such as daily exercises are stressed. An instance of severe edema following femoral vein ligation in thrombophlebitis is described. The great advantage of the anticoagulant method is that thrombosis and phlebitis are controlled in all parts of the body and not just in the legs. Patients with thrombophlebitis should not be kept in bed too long. In arteriosclerotic disease of the extremities, patients are encouraged to walk at a leisurely pace from one to three miles daily, and other activities such as dancing, golf, and riding a bicycle, are advised within reasonable limits. These exercises seem indicated because the active use of a muscle tends to produce an increase of its blood supply. When amputation is indicated, mid-leg amputation, rather than amputation above the knee, is advised in nearly all cases because of the greatly reduced mortality. In the management of the patient with thromboangiitis obliterans, tobacco must be given up completely and permanently. The author believes that amputations for this disease could be absolutely eliminated if thromboangiitis were always recognized and treated in its early stages and if patients cooperated by ceasing to use tobacco when instructed to do so.

NAIDE.

Eisen, Herman N.: Primary Systemic Amyloidosis. Am. J. Medicine **1**:144 (Aug.), 1946.

Two case reports of primary systemic amyloidosis are presented with detailed autopsy findings and a review of the literature. In each patient the presenting manifestations were macroglossia, profound asthenia, and, ultimately, death in congestive heart failure.

Analysis of the symptomatology of forty-eight cases revealed that congestive heart failure occurred in 54 per cent and macroglossia and asthenia in 42 per cent.

In forty-six autopsied cases amyloid was found in the myocardium in 85 per cent and with somewhat less frequency in the endocardium (61 per cent), pericardium (48 per cent), valves (37 per cent), and in other organs.

Although exceptions occur, primary amyloid disease is characterized chiefly by involvement of the heart, tongue, gastrointestinal tract, and skeletal muscle. It affects middle-aged or elderly individuals, begins insidiously, is slowly progressive, frequently gives a negative Congo red test, and is not associated with chronic infection. Diagnosis is best established by biopsy but difficulty may be encountered in that the amyloid deposits have a variable affinity for the amyloid stains.

The age incidence, organ incidence, and atypical staining properties of the amyloid deposition associated with multiple myeloma resemble closely that seen in primary amyloidosis. In the latter, however, there is no hyperglobulinemia.

In contrast, amyloidosis secondary to chronic infection is characterized by a relatively high incidence of involvement of the kidney, spleen, liver, and adrenals, and only rarely the heart, tongue, gastrointestinal tract, or skeletal muscle. Also secondary amyloidosis runs a shorter course, occurs most frequently in young adults and rarely in middle life, and yields more consistent and typical results with the amyloid dyes.

The pathogenesis of the disease is unknown. FRIEDLAND.

Silverman, S.: Vascular Tumours of the Spinal Cord Associated With Skin Hemangiomata. Brit. M. J. **33**:307 (April), 1946.

A case is described of a vascular extradural spinal cord tumor, at the level of the sixth to tenth thoracic segments, in a woman 47 years old, who also had a very extensive congenital nevus, involving the fifth cervical to tenth thoracic dermatomes on the left side. The presence of the tumor was confirmed by operation.

The possibility of the presence of a vascular abnormality in the corresponding segment of the spinal cord should be kept in mind in patients who present a nevus of the skin together with signs and symptoms of a spinal cord lesion. Although malformations of the spinal cord, similar to and usually in the same segment as that of the skin condition, may be present, as a result of disturbance of mesenchymal development, their presence may not be suspected until either hemorrhage occurs or they increase in size, as in the case described.

Cases of vascular tumors of the spinal cord associated with skin hemangiomas which have been recorded in the literature are reviewed. Most of them are of a simple hemangiomatosis nature, corresponding to the skin condition, rather than hemoblastomatous. NAIDE.

Falconer, M. A., and Lindsay, J. S. B.: Painful Phantom Limb Treated by High Cervical Chordotomy. Brit. J. Surg. **33**:301 (April), 1946.

Pain occurring in a phantom limb has the same characteristics as causalgia occurring in an intact limb with a peripheral nerve injury. There are two main groups of cases. In one group pain impulses appear to arise in or around the neuromas or the divided nerves and can be relieved by excision of the neuromas or by sympathetic block or by sympathectomy. In the other group, painful impulses arise in the dorsal horn cells of the spinal cord and can be relieved only by section of the spinothalamic tract or by excision of the sensory cortex of the cerebrum. Infiltration of the appropriate peripheral or sympathetic nerve pathways with a local anesthetic solution is a useful diagnostic procedure for distinguishing clinically between these two groups. When these diagnostic tests fail to give relief, section of the spinothalamic tract is indicated and seems preferable to ablation of the sensory cortex, because it does not destroy the phantom or the patient's appreciation of his stump, but only abstracts from it the sensation of pain.

Two cases are described which illustrate these points. In both patients an arm was amputated above the elbow, as the result of wounds by a shell in one patient and by a bullet in the second. In both patients a cut was made in the cervical cord between the first and second cervical nerve roots to a depth of 4 millimeters. The phantom limb pain was completely relieved. There was no subsequent loss of sensation of touch, posture, vibration, or two-point discrimination. In each patient the only disability that remained was the loss of the limb. NAIDE.

Bates, Robert R.: Surgical Aspects of Trench Foot. Surg. Gynec. & Obst. 83:243 (Aug.), 1946.

The author's experience with 264 cases of trench foot which required surgery is recorded. Many additional patients who came under his care had only a temporary superficial gangrene of the skin of the toes which recovered spontaneously. Most patients lost only parts of several toes. Eleven, however, lost all toes of at least one foot and thirty-two lost some or all of the metatarsal heads as well. It was found useful to adhere to certain surgical principles. Surgery was delayed until all possible spontaneous recovery had occurred. This policy resulted in the saving of toes and feet. Grafted skin was found unsuitable for covering the stumps. The advantages of covering a stump with a flap of normal weight-bearing type plantar skin outweighed the advantages of retaining metatarsal heads. Contrary to general surgical opinion, removal of some or all metatarsal heads was found not to handicap the function of the foot too seriously. A postoperative reactive hyperemia on a traumatic basis is described and contrasted with postoperative cellulitis due to infection. Preoperative and postoperative active exercises help to prevent shortening of heel cords and correct fibrotic contracture of toes. A prosthesis designed to be part of a shoe insert, often combined with a longitudinal arch support, is described.

NAIDE.

Waife, Sholom O., and Pratt, Peyton T.: Fatal Mercurial Poisoning Following Prolonged Administration of Mercurophylline. Arch. Int. Med. 78:42 (July), 1946.

A case of fatal mercurial poisoning following prolonged administration of mercurophylline is reported. As far as the authors could determine, this is the first reported case of a mercurial toxic nephrosis with anuria and death which followed the usual course of repeated parenteral injections of mercurophylline. The patient was a 35-year-old woman with rheumatic heart disease and congestive failure, who received mercurophylline parenterally for six months and who developed an acute anuria which proved fatal in spite of bilateral decapsulation of the kidney. Post-mortem examination revealed nephrosis, hemorrhage in the ileum and colon, and focal areas of necrosis and hemorrhage in the liver. Mercury was found in the liver and kidney. Death was attributed to mercurial intoxication.

The problem of the treatment of anuria of this type is still unsettled. Large amounts of fluid are usually administered, although there is some evidence that restriction of fluid intake and bilateral renal decapsulation may be of value. This issue has recently been reopened by Peters who believes that the factor which inhibits the flow of urine is an increase in intrarenal pressure and not a low arterial pressure or tubular blockage by detached necrotic cells. BELLET.

Smirnova-Zamkova, A. I.: Significance of Basic Argyrophil Substance in the Pathogenesis of Hypertension. Am. Rev. Sov. Med. 3:534 (Aug.), 1946.

The argyrophil substance which enters into the composition of the hematoparenchymal barrier is stated to be a part of the physiologic connective tissue. It is situated between the epithelial structures and the subjacent connective tissue, as well as in the vascular walls, and forms an outer and inner filtering membrane. This substance exists in both a sol and a gel state and is able to pass from one state to the other in the presence of disease processes.

Studies were made on a series of twenty-five human subjects with hypertension and twelve rabbits in which experimental hypertension had been produced. Following silver impregnation of the vascular tissues, certain changes in the basic argyrophil substance were found. The media of the small vessels and the capillaries became permeated by thickened argyrophil membranes. Stenosis of the lumen occurred in advanced cases. The argyrophil filtering membranes of capillaries, small veins, and arterioles were condensed, thickened, and coarsened. This was most evident in vessels of the heart, lungs, and in the vasa vasorum. The changes are considered characteristic of the pathomorphology of hypertension. In the large vessels, coarsening of these membranes was more marked in the adventitia. Early in the course of hypertension, the condensation and thickening of the argyrophil fibers may dissolve; in the final stage of hypertension, generalized

fibrosis takes place and the organs shrink following the extensive condensation of the basic argyrophil substance. The changes occurring in the experimental animals and man were identical. The author views these changes as a causative factor in hypertension. BELLET.

Homans, J.: The Late Results of Femoral Thrombophlebitis and Their Treatment. New England J. Med. **235**:249 (Aug. 22), 1946.

Femoroiliac thrombophlebitis is the usual end stage of thrombosis of the deep veins of the leg. Patients may be classified into five groups according to the following clinical criteria. In Groups 1 and 2, the predominant characteristic is edema, with or without pigmentation, induration, or ulceration. Local allergic inflammation and saphenous varicosity are often contributing factors. These patients are best treated by rest, elevation of the limb, muscular exercise, semielastic stockings, local treatment of the skin and nails, and, in some instances, by section or excision of varicose veins. The use of sclerosing injections is considered to be uniformly harmful. In Group 3 a pain complex, with or without associated vasomotor changes of the skin and stocking-like parasthesias, is the predominant characteristic. Lumbar sympathetic block is effective. Sympathectomy may be employed in obstinate cases. In Group 4, the outstanding feature is marked venous congestion, with cyanosis and prominent surface veins. Contrary to views widely held in the past, the author finds surgical division of the deep veins a highly useful procedure. Group 5 has as its chief characteristic recurrent thrombosis of the deep veins. Such episodes may last for a period of years. The therapeutic procedure of choice is ligation of the common iliac vein. KAY.

Russakoff, A. H., and Katz, H. W.: Dextrocardia and Bronchiectasis. New England J. Med. **235**:253 (Aug. 22), 1946.

The authors re-emphasize the observation that congenital dextrocardia is not always a completely benign disorder. References are cited to indicate that bronchiectasis is present in from 16 to 23 per cent of these patients, and that chronic sinusitis occurs with unusual frequency. They report two cases of dextrocardia with bilateral bronchiectasis, chronic sinusitis, and transposition of the abdominal viscera. KAY.

Houston, C. S.: The Effect of Pulmonary Ventilation on Anoxemia. Am. J. Physiol. **146**:613 (July), 1946.

Normal subjects breathed a mixture of approximately 10 per cent oxygen in nitrogen. Respiratory minute volume, arterial oxygen saturation, alveolar and arterial pO_2 and pCO_2, and arterial pH were measured. Each subject was required to breathe a given oxygen mixture at several different levels of minute volume. It was found that the arterial oxygen saturation could be increased significantly by voluntarily increasing the minute volume. For example, one subject's arterial oxygen saturation was 64 per cent while breathing the low oxygen mixture at a rate of 10 liters per minute; at 17.5 liters per minute the arterial oxygen saturation rose to 85 per cent.

At the higher levels of ventilation, alveolar and arterial pO_2 and arterial pH rose, whereas alveolar and arterial pCO_2 fell.

It is suggested that the influence of changes in pulmonary ventilation must be evaluated in any clinical study of anoxia. FRIEDLAND.

Goldberger, E.: Significance of Downward T Wave in Precordial Leads of Normal Children. Am. J. Dis. Child. **71**:618 (June), 1946.

Four-lead electrocardiograms were taken on 50 normal children and the group that showed T-wave inversion (18 per cent of the 50) were selected for further investigation. This group was studied by the use of six precordial leads taken with the author's indifferent electrode of zero potential. Precordial leads that faced the epicardial surface of the right ventricle showed either a positive or negative T wave which was associated with an RS type of ventricular complex. Leads facing the epicardial surface of the left ventricle showed a positive T wave only, which was usually

associated with a qR or qRs type of ventricular complex. A qR pattern associated with a downward T wave in a precordial lead is regarded as being always abnormal.

There is presumably more right ventricular surface facing the chest wall in childhood and this is believed to account for the greater frequency of T-wave inversion in the electrocardiograms of normal children. HAUB.

Rosenkrantz, J. A., and Bruger, M.: Experimental Atherosclerosis: II. The Effect of Prolonged Feeding of Egg Yolk Powder in Rats. Arch. Path. **42**:81 (July), 1946.

The feeding of egg yolk powder to rats for prolonged periods produced hypercholesteremia but no atherosclerosis. The authors suggest that lecithin, because of its choline content, inhibited the deposition of cholesterol in the aorta. The cholesterol and fat content of the liver were increased. To explain this discrepancy in the protective action of lecithin against lipoid deposit in the aorta and its failure to protect the liver, the authors postulate that a diet consisting wholly of egg yolk powder is inadequate in those substances, such as are found in yeast or other sources of vitamin B complex, which ordinarily act to protect the liver.

The rats fed egg yolk powder failed to show an increase in systolic blood pressure or any evidence of vascular damage. GOULEY.

Deutsch, A., and Lundin, G.: The Effect of Minute Amounts of Barium on Cardiac Muscle. Acta. Physiol. Scandinav. **11**:373, 1946.

Small amounts of barium salts had a striking effect in initiating contraction in a threaded frog heart muscle preparation after a brief period of increased excitability. The contractions lasted several minutes. Strontium had about one-fiftieth the activity of barium, while other metallic ions had none. Calcium and magnesium salts increased the strength of contraction, while sodium salts diminished or abolished it. Adenosine triphosphate was found to be inactive in increasing the excitability of heart muscle in contrast to its recognized effect on skeletal muscle. Reports of its cardiac muscle action were occasioned by the use of its barium salt and the effect is now believed to have been due solely to the barium. SAYEN.

Lundin, G.: The Influence of G-Strophanthin on the Mechanical Properties of Cardiac Muscle. Acta. Physiol. Scandinav. **11**:221, 1946.

The action of G-strophanthin on normal heart muscle was studied in a parallel threaded frog ventricular muscle preparation. The contraction of the muscle, held between silver tweezers which served as the stimulating electrode, was measured by a condenser myograph. It was found that the drug had no effect on diastolic tension, extra tension during contraction, stiffness at rest and during contraction, viscosity, or the capacity for work during isometric contraction. SAYEN.

Griffith, G. C., and Huntington, R. W.: Sudden Death in Rheumatic Fever. Ann. Int. Med. **25**:283 (Aug.), 1946.

The present report concerns three cases of sudden death which occurred among a group of 7,165 patients with active rheumatic fever at the active rheumatic fever unit of the United States Naval Hospital at Corona, Calif. The three deaths were sudden, unexpected, and dramatic. Histologic studies showed unquestionable evidence of active rheumatic carditis.

A common and striking feature of the three cases was the presence of destructive lesions at the base of the aorta. In two of the cases there was unequivocal evidence of widespread vascular disease, particularly in the coronary and pulmonary arteries. Most of the changes appeared to be relatively acute.

It is believed by the authors that the cause of abrupt death in the three cases was due to an acute and anaphylactic coronary angiitis superimposed upon a low-grade rheumatic carditis. WENDKOS.

Gold, M. M. A.: Congenital Dilatation of the Pulmonary Arterial Tree: Relation to Ayerza's Disease and Primary Pulmonary Arteriosclerosis. Arch. Int. Med. **78**:197 (Aug.), 1946.

Congenital dilatation of the pulmonary artery as a single lesion unaccompanied by other developmental anomalies appears to be an extremely rare condition. It is referred to by this author as "isolated congenital dilatation of the pulmonary arterial tree." Its diagnosis is based on the following criteria: dilatation of the entire pulmonary arterial tree with or without sclerosis; hypoplasia of the aorta; absence of other congenital anomalies; absence of other primary disease of the heart, lungs, or arteries. When these criteria are applied, only four cases in the literature meet the requirements for the diagnosis of congenital dilatation of the pulmonary artery.

A case is reported which meets the above criteria. The patient was a 41-year-old white woman who had had two attacks of circulatory failure seven years prior to admission. Four years prior to admission she first noticed cyanosis of the fingertips. Physical examination on admission revealed cardiac enlargement, a systolic thrill over the entire precordial region, and a systolic murmur to the left of the sternal border. The electrocardiogram showed right axis deviation. Fluoroscopic examination revealed dilatation of the pulmonary artery, increased pulsation of the pulmonary vessels, and hypertrophy of the right ventricle. The temperature increased to 102°, and a blood culture was positive for *Streptococcus viridans*. The clinical diagnosis was bacterial endocarditis and patent ductus arteriosus. Necropsy showed right ventricular hypertrophy. The pulmonary artery was enlarged and its branches were dilated. Arteriosclerotic changes were found throughout the entire pulmonary arterial tree. Large numbers of the smaller vessels showed concentric fibrous thickening of the intima. From the description, this case may be considered to represent one of three conditions: Ayerza's disease, primary pulmonary arteriosclerosis, or isolated congenital dilatation of the pulmonary artery. The author points out that some of the cases reported as Ayerza's disease are merely examples of secondary sclerosis of the pulmonary artery, others are instances of primary pulmonary arteriosclerosis, and a few are cases of congenital dilatation of the pulmonary arterial tree. BELLET.

Orning, K., Sommerfelt, C., and Fredriksen, W.: Electrocardiographic Findings in Patients with Peptic Ulcers. Acta. Med. Scandinav. **124**:564, 1946.

Among 579 patients with peptic ulcer but without heart disease (63 per cent of whom were men), electrocardiography showed sinus bradycardia to be common, especially in men below the age of 40. In women the rate was rarely less than 45 per minute but in men rates in the high thirties were not infrequent. Sinus arrhythmia was relatively more common in women and usually was associated with bradycardia. The most striking electrocardiographic feature was a high T wave (greater than one-half the height of the R wave in at least two leads) which occurred in 60 patients (52 of whom were men). Occasionally the T wave attained a height of 0.9 centimeter. The S-T segment was elevated in 37 of the 60 patients, especially in Lead II. Nine patients showed top-normal or slightly prolonged P-R intervals. Belladonna and diet caused partial or complete disappearance of the above changes in almost all cases, and the authors believe that the changes were the result of vagotonia.

In 74 cases in which hemorrhage had occurred, 35 per cent had "pathologic" tracings. The changes consisted chiefly of flattened T waves and depressed RS-T segments in Leads II and III without QRS changes. These appeared too promptly to be attributed to the relatively slight anemias that were present, and none of the patients had a significant fall in blood pressure. The changes were thought due to a vasomotor reflex affecting the coronary circulation, with consequent myocardial anoxemia. SAYEN.

Munck, W.: The Pathological Anatomy of Sudden Heart Death. Acta Path. et Microbiol. Scandinav. **23**:107, 1946.

Of 500 cases of sudden cardiac death subjected to legal autopsy at Copenhagen 82 per cent were males. The author believes this figure to be of little significance since more men than women die under conditions of interest to police or insurance companies. The general Danish mortality

statistics report an approximately equal incidence of cardiac deaths in the two sexes. In 79.2 per cent of the cases, death was associated with coronary disease and its sequellae. Syphilitic aortitis accounted for 11 per cent; the majority of such cases showed no myocardial change. Valvular disease, usually aortic stenosis, appeared to be the cause of sudden death in 3.8 per cent and congenital defects in 1.8 per cent, while myocarditis was comparatively rare.

Of the patients with coronary disease, one-fifth showed no myocardial change and no arterial occlusion. Another 35.6 per cent showed thromboses, three-fourths of these being in the left coronary artery, in which the commonest sites of occlusion were in the first 2 centimeters of the left anterior descending ramus. The right coronary artery was usually occluded farther from its origin. Occlusions of the left circumflex branch were uncommon. Acute infarction was found in 18.7 per cent of the coronary group, almost one-half of these being associated with previous scarring. Two-thirds of the infarcts were anterior. The frequency of strenuous exertion preceding infarction is stressed. Most trombi had formed on atheromatous ulcers, but a few were associated with mural hemorrhage. Cardiac rupture occurred in 26 cases. Of these, 15 were on the anterior and eight on the posterior aspect of the left ventricle, while three were in the right ventricle. The author was impressed by the frequency of atheromatous changes in the coronary arteries in persons over 40 years old. These changes were most marked in the left anterior descending ramus where the process seemed relatively more advanced than in the aortic wall or the arteries of the brain. SAYEN.

Burdick, D. L., Phelps, McK. L., and Peterson, M. C.: Anesthesia for Sympathectomy in Hypertension. N. Y. State J. Med. **46**:2139 (Oct.), 1946.

With the more extensive surgery now being employed for sympathectomy, in hypertension, responsibility for the anesthetic management becomes proportionately greater. The present tendency is toward a more radical surgical procedure which may include the removal of ganglia as high as the third or fourth dorsal. It has become almost a matter of certainty that at some stage during surgery, the parietal pleura will be entered. The administration of the anesthetic must be planned with the anticipation of an open thorax and a collapsed lung. The present trend favors minimal medication with depressant drugs to permit spontaneous breathing, except when the controlled method is indicated. Use of the endotracheal technique is important, the choice between the oral or nasal route is not. A period of hypoxia, or actual anoxia, attendant upon a difficult or traumatic intubation is a serious complication.

Both during and following surgery, especially after the second stage, episodes of circulatory depression are not infrequently observed. At this period the development of pulmonary edema should be anticipated and measures taken for its prevention and treatment.

Neosynephrine continues to be the most valuable remedy for blood pressure disturbances. These authors believe that the prevention of sudden, severe hypotension in certain stages of the operation may be accompanied by starting an infusion of 5 per cent glucose in water or saline as soon as the patient is placed in the operating position. Neosynephrine, 0.02 Gm. per liter, is added to the solution, and the flow started at approximately 60 drops per minute. Regulation of the rate of flow permits a flexible means for controlling the amoung of drug given in accordance with the varying needs. This method maintains a fairly even blood pressure throughout surgery and during the immediate postoperative period. At the conclusion of the continuous intravenous, neosynephrine, 0.0013 Gm. (2 minims) is given and repeated as needed if severe hypotension occurs. The authors believe that the administration of large amounts of plasma, a procedure frequently employed in the operating room, is contraindicated because the physiologic disturbances incident to sympathectomy are not due to any appreciable loss of circulating fluid from the body but to the dilatation of a considerable portion of the vascular bed, which can be controlled adequately by sympathomimetic drugs until the body mechanisms become adequately adjusted. BELLET.

Schlichter, J. G.: Experimental Medionecrosis of the Aorta. Arch. Path. **42**:182 (Aug.), 1946.

The author produced experimental medionecrosis of the aorta in dogs by coagulating the adventitia of the ascending aorta with heat. The site of coagulation was that area of the ascending aorta where anastomosis of the vasa vasorum from different main vessel origins is most pronounced. This was done in seven dogs weighing 20 to 30 pounds each. They were permitted to recover from the anesthesia and were killed in one, two, or six weeks.

In addition, a dog previously made hypertensive by daily injections of desoxycorticosterone acetate and prolonged drinking of 1 per cent salt solution, was similarly subjected to heat coagulation of the adventitia of the ascending aorta. This dog was killed in six weeks. Another hypertensive dog was used as a control.

A group of four dogs was studied six to twelve hours after coagulation. In all dogs the vasa of the aorta were injected and then examined by x-ray visualization.

In the dogs studied six to twelve hours after adventitial coagulation, there were no gross changes but microscopy revealed small hemorrhages in the outer third of the media. The inner third showed marked edema with separation of the elastic and muscle fibers. There was no cellular infiltration in the media.

One week after operation, the aorta showed yellowish brown areas in the media, not only beneath the coagulated adventitia but also 1 to 2 cm. distant from the area of coagulation.

Two to six weeks postoperatively, these yellow-brown areas were partially replaced by grayish areas which extended to the intima. One dog, whose postoperative course was marked by apathy and anorexia showed at autopsy a dissecting aneurysm of the ascending aorta with rupture 2 cm. above the aortic cusps.

At the end of one week, microscopy showed diffused necrosis of the outer and middle thirds of the media, evidenced by loss of nuclei and swelling of the elastic fibers. Areas of liquefaction with cyst formation with or without mucoid material were observed. Uneven involvement was attributed to anastomotic preservation of small blood vessels. In the second week, further loss of elastica was noted, and at the same time replacement of cystic and necrotic areas by young fibrous tissue and collagen deposit. This reparation process was pronounced in the sixth week. Fibrous tissue growing into the adventitia was richly vascularized. The changes in the hypertensive dog were the same, but the intimal thickening was much more marked. The control hypertensive dog showed no abnormal changes.

The author believes that the rich vascularization of the aortic adventitia prevents necrosis which occurs only when the entire circulation to a given area is destroyed. In the delayed subnecrotic response to this type of operation, the changes in the media are featured by cyst formations and mucoid degenerations. "Medionecrosis cystica idiopathica" has been ascribed by some workers to ischemia following circulatory disturbances of the vasa vasorum. The results of coagulation-necrosis of the aortic adventitia with destruction of many vasa vasorum is, according to Schlichter, a positive demonstration of the importance of the ischemia factor. GOULEY.

Farinas, P. L.: Retrograde Abdominal Aortography. A Contribution to the Study of the Abdominal Aorta and Iliac Arteries. Radiology **47**:344 (Oct.), 1946.

Simple roentgen examination of the abdominal aorta and iliac arteries offers information only in the presence of calcification of the arterial walls or calcified aneurysms. Retrograde abdominal aortography is a simple method for the study of all the pathologic changes of the aorta and iliac arteries. This method consists in exposure of the femoral artery by blunt dissection under local anesthesia at the level of Scarpa's triangle and its puncture with a trocar 1.5 mm. in diameter through which are injected 50 c.c. of a 70 per cent solution of diodrast in two and one-half to three seconds. A tourniquet is applied at the root of each lower extremity in order to prevent the passage of the contrast medium into their arteries. With a trocar 1.5 mm. in diameter and a constant pressure of 15 pounds, it is possible to inject 25 c.c. of the opaque substance per second, the speed of injection being modified according to the blood pressure and vascular condition of the patient. The diagnosis of syphilitic disease of the abdominal aorta and iliac arteries is suggested by dilatation or occlusion of the lumen. Degenerative lesions are also frequently

observed by this method, which may disclose dilatation, elongation and tortuosity, including complete obliteration of the lumen. This author believes he is the first to have demonstrated valvular kinks in the iliac and femoral vessels which retard the circulation considerably. Surgical removal of these valvular kinks was shown to benefit greatly the circulation of both extremities. He hopes that this procedure will contribute to a better knowledge of the pathologic condition of these vessels and thus offer new approaches to treatment. BELLET.

Schwarz, G. S.: Determination of Frontal Plane Area from the Product of the Long and Short Diameters of the Cardiac Silhouette. Radiology 47:360 (Oct.), 1946.

The material upon which this study was based consisted of 99 teleroentgenograms made on 93 subjects. Group I consisted of 25 films of normal subjects (10 males and 15 females) ranging in age from 7 to 54 years; in weight from 18 to 118 kg., in height from 132 to 177.5 cm., and in cardiac area from 72 to 145.5 square centimeters. Group II consisted of 74 films made on 68 subjects in whom clinical or x-ray evidence indicated heart disease. Thirty-five were males and 33, females. The ages varied from 6 to 82 years, the weight from 14.1 to 88.9 kg., the height from 100 to 185 cm., and the cardiac area from 50 to 282 square centimeters.

The films were made with the subject standing or sitting facing a vertical cassette changer and with a target film distance (D) of approximately 6 feet. The silhouettes were outlined with wax pencil on the film and then transferred to semitransparent paper for planimetric measurement of area and linear measurements of the long and short diameters. For each case the product of these diameters was divided into the area of the silhouette, the quotient being a factor which is indicated as F. For the normals the mean value of F was 0.740; for the abnormals, 0.730; the average 0.735 was therefore chosen as the factor for general application. On this basis the calculation of frontal plane area from long and short diameter becomes

$$A = L \times S \times 0.735$$

where A is the gross frontal plane area of the heart in sq. cm. in full-sized roentgenograms made with the patient facing the film at a target-film distance of approximately 72 inches; L, the long diameter of the cardiac silhouette in cm.; S, the short diameter of cardiac silhouette in centimeters.

Investigation of the accuracy of this formula revealed the maximum deviation to be −4.7 per cent and − 6.5 per cent, the minimum deviation zero. This indicates that the formula $L \times S \times 0.735$ is more accurate than the ellipse formula. Three monograms are provided to facilitate application of the various formulas. These yield net frontal plane area and also the amount by which this value varies from normal. BELLET.

Hodges, P. C.: Heart Size from Routine Chest Films. Radiology 47:355 (Oct.), 1946.

The systolic size rarely is recorded on routine chest films and the larger shadow in a pair of such films may be accepted as of approximately diastolic size. Hodges measured the gross frontal plane area from the larger of the two shadows in routine chest films and then corrected this value for divergent distortion. If the net frontal plane area thus obtained is within plus or minus ten per cent of the normal area predicted from the patient's height and weight, it is reported as normal, with the actual percentage variation from normal added in brackets. Because of a divergent distortion that is always present in ordinary roentgenograms, gross area is greater than true or net frontal plane area, the latter being obtained from the former by multiplying gross area by a correction factor F, obtained from the equation:

$$F = \left\{1 - \frac{K}{D} - \frac{C}{3D}\right\}^2$$

In this equation, F is the divergent distortion correction factor; K, the distance in centimeters between anterior surface of chest and film; D, the distance in centimeters between target of x-ray tube and surface of film; C, the anteroposterior diameter of chest in centimeters (varies from approximately 5 cm. to 28 cm. depending upon the patient).

Computations would be far too tedious if they had to be done for each examination, but by reducing the various equations to alignment charts or nomograms, all computations are avoided. The author concludes that although the best way to determine the size of the frontal plane area is to measure it with a planimeter, without much sacrifice of accuracy, one may simplify the technique by measuring the long and the short diameters and multiplying their product by the factor 0.735. BELLET.

Crosby, R. C., and Cooney, E. A. Surgical Treatment of Ascites. New England J. Med. **235**:581 (Oct. 17), 1946.

The literature concerning omentopexy, nephrectomy with anastonosis of the renal pelvis to the peritoneum, and portocaval shunts in the treatment of ascites is reviewed. The authors describe five cases of portal cirrhosis and one of constrictive pericarditis in which the ascites was relieved by the insertion of a hollow glass button into the lower rectus sheath so that ascitis fluid drained from the peritoneal cavity into the subcutaneous tissues and was absorbed as edema fluid. They were unable to ascertain the originator of this method. The need for repeated abdominal paracentesis and the attendant loss of protein was obviated. Four of the five patients with cirrhosis were greatly improved. Edema of the abdominal wall and thighs continued to be a troublesome sequel in the patient with constrictive pericarditis. KAY.

Segall, E. L., Kurland, G. S., and Riseman, J. E. F.: The Effect of Age on the Clinical Effectiveness of Nitroglycerin Tablets. New England J. Med. **235**:650 (Oct. 31), 1946.

Current medical opinion recommends that patients employing nitroglycerin for the treatment of angina pectoris discard old tablets and purchase fresh ones every three to six months. The controversial results of chemical assays of nitroglycerin tablets at varying times after manufacture are cited. The authors performed biologic assays of fresh tablets, of tablets stored at room temperature for periods as long as eleven years, of tablets incubated at 37°C. for three months, and of tablets contained in loosely-capped vials carried in vest or trousers pockets for a period of four months. The test subjects were patients with angina pectoris. For each patient the amount of exercise required to induce pain was a known constant, which could be measurably increased after the sublingual administration of nitroglycerin. As a result of this study the authors conclude that there is no essential loss of clinical potency in old tablets stored at room temperature for many years, or of tablets carried by patients in the customary manner for four months, but that fresh tablets stored for three months at 37°C. become completely ineffective clinically. KAY.

Dean, J. V. B.: Relation of Cardiac Enlargement to Hypertension in Acute and Chronic Glomerulonephritis. Am. J. Med. **1**:161 (Aug.), 1946.

The author reemphasizes the absence of a correlation between heart size and arterial blood pressure in patients with chronic glomerulonephritis. The cardiothoracic ratios of three normotensive patients with chronic glomerulonepheritis varied between 0.55 to 0.64 over eight to nineteen years of observation. On the other hand, the cardiothoracic ratios of three hypertensive patients with chronic glomerulonephritis remained at 0.51 or less over a two- to five-year period of observation. In these latter patients the cardiothoracic ratios did not reach or exceed 0.50 until their disease had progressed to its terminal phase.

It is concluded that cardiac enlargement in patients with long-standing chronic glomerulonephritis is not necessarily related to coexisting hypertension. FRIEDLAND.

Pardee, H. E. B., and Goldenberg, M.: Electrocardiographic Features of Myocardial Infarction as Affected by Involvement of the Septum and by Complete and Incomplete Transmural Involvement. Arch. Inst. cardiol. México **16**:109, 1946.

The authors believe that many of the current theories regarding the cause of electrocardiographic changes after myocardial infarction need revision. They therefore reviewed the clinical

records and autopsy findings of 11 patients who died soon after a myocardial infarction, and one patient who died two years later. This study led to the following conclusions:

1. Rotation of the electrical axis of the QRS complex toward the right may occur after either anterior or posterior infarction but occurs more uniformly after the latter.

2. The typical S-T and T-wave changes occur most often when necrosis of either the anterior or the posterior wall is associated with a lesion of the septum. When the septum is undamaged, the typical changes occur less constantly

3. The typical S-T and T-wave changes in both the limb and precordial leads and the QRS complex changes in the precordial leads may appear occasionally after anterior infarction even if the subepicardial layers are unaffected; usually, however, there is definite evidence of involvement of the subepicardial layers.

4. A Q or Q-S wave in the precordial leads is associated with necrosis of the anterior part of the septum. It may be present when the latter is not accompanied by involvement of the anterior wall.

5. A complete transmural lesion may be accompanied by a deep Q wave in Lead III even without involvement of the posterior part of the septum.

6. The records of cases with anterior infarction but no subepicardial necrosis resemble those seen after exercise and anoxemia tests and during anginal attacks. LUISADA.

Fox, T. T., Sokol, D. D., and Bernstein, I. J.: The Significance of Concordant Inverted Initial Ventricular Deflections in the Electrocardiogram of Patients With Pulmonary Tuberculosis. Quart. Bull. Sea View Hosp. **8:95** (April), 1946.

The significance of electrocardiograms which show concordant QRS complexes is not clear. Some believe these to be the result of myocardial damage occurring either alone or in association with rotation of the heart around its longitudinal axis. These authors observed fourteen patients who exhibited this condition. In twelve of these the concordant feature was caused by S waves. In two patients, the concordant downward deflections were caused by Q waves; these two patients had had acute coronary occlusion. There were three more cardiacs in this group of fourteen patients; one with evidence of impairment of the conduction mechanism, one with radiographic evidence of heart enlargement, and a third with hypertension.

In evaluating the significance of the downward QRS deflection it is essential to differentiate between the Q and S type of electrocardiogram. It is the conclusion of these authors that the presence of concordant downward deflection of the QRS group caused by S waves is neither an indication of heart disease nor of prognostic significance. Spontaneous and artifically produced variations in the form of the QRS complexes in some of the cases speak in favor of the phenomenon being a function of the position of the heart within the thorax. The Q-type of tracing is usually indicative of a coronary occlusion, and has a definite prognostic value. BELLET.

Stokes, W.: The Effect of Nitrites and Exercise on the Inverted T Wave. Brit. Heart J. **8:62** (April), 1946.

In practice, the similarity of the T_1 type of cardiac infarction and the inversion of the T wave from hypertension or aortic valvular disease presents a common problem in differential diagnosis. Observations were therefore made on the effects of nitrite and exercise on the inverted T wave in order to evaluate the help that such tests might afford in deciding this problem.

Forty-five patients whose electrocardiograms showed deformity of the T wave were studied. The electrocardiogram was recorded before and after (1) a standardized inhalation of amyl nitrite and (2) a standardized exercise test which consisted of bending repeatedly to touch the toes, or raising and lowering the legs with the knees straight while the subject reclined on a couch, the exercise being continued to the point of fatigue.

Amyl nitrite inhalation was followed by correction of inverted T waves in six of sixteen cases of cardiac infarction and seven of thirteen cases of hypertension but the T wave inversion was not corrected in any of seven cases of aortic valvular disease. Exercise similarly righted the inverted T waves in nine of sixteen cases of myocardial infarction and in two of thirteen cases of hypertension but did not correct the T wave inversion in any cases of aortic valvular disease.

It was concluded that tests involving amyl nitrite inhalation, exercise, or change of posture do not differentiate the T wave inversion of myocardial infarction from that of hypertension. It is not certain that these procedures alter the T waves by relieving myocardial ischemia since their effect in cases of hypertension is similar to that in myocardial infarction. LAPLACE.

Ellis, L. B.: Electrocardiographic Abnormalities in Severe Malnutrition. Brit. Heart J. **8**:53 (April), 1946.

Serial electrocardiograms were made in a series of thirteen liberated American prisoners of war who had been starved by their German captors and whose condition was critical. Clinical examination revealed severe malnutrition but there were no definite manifestations of avitaminosis or anoxia of the heart muscle.

The cardiographic changes consisted of a marked prolongation of the Q-T interval, unusually well-marked but not persistent U waves, and, less constantly, depression of the S-T segment, alterations of the T waves, and increase in the P-R and QRS intervals.

It was concluded that the electrocardiographic changes in malnourished subjects probably represented a composite picture due to prolonged protein and carbohydrate starvation and electrolyte imbalance. The fact that the cardiograms returned to normal within two or three weeks after institution of adequate therapy suggests that the changes are chiefly due to functional and not to strutural causes. LAPLACE.

Szekely, P.: The Action of Magnesium on the Heart. Brit. Heart J. **8**:115 (July), 1946.

Magnesium appears to have a depressant action on the heart but there is no general agreement about the mechanism of this action and there are few reports dealing directly with the clinical application of its cardio-inhibitory properties. Observations were therefore made on the effect of intravenous injection of 20 c.c. of a 20 per cent solution of magnesium sulfate on the electrocardiogram in twenty-six cases in which the diagnoses included paroxysmal tachycardia, auricular fibrillation, and extrasystoles.

Magnesium produced only minor changes in the normal cardiogram. It affected nine of thirteen cases of paroxysmal tachycardia; in five of the nine cases, the effect was lasting and in four only temporary; in the remaining four cases, variable degrees of A-V block appeared. Extrasystoles caused by full digitalization were either completely obliterated or altered by magnesium sulfate while extrasystoles from other causes were not affected by it. Magnesium had no effect on auricular fibrillation.

It is concluded that magnesium in the dosage used in this study has no appreciable effect on the normal conduction system. It may depress impulse production in heterotropic centers and, in the presence of increased myocardial irritability, all parts of the conduction system may be depressed. The data presented justify the use of magnesium sulfate as a therapeutic agent in paroxysmal tachycardia; it is a safe procedure but its effect may be only temporary.

LAPLACE.

Evans, W.: The Heart in Sternal Depression. Brit. Heart J. **8**:162 (July), 1946.

The author studied sixteen patients who had depression of the sternum and had been referred because of supposed heart disease. In none of the patients, however, were the symptoms the result of cardiac enlargent or insufficiency. They were in all cases attributable to physical inactivity or anxiety resulting from unwarranted invalidism.

The cases were separated into three groups according to the degree of sternal deformity: funnel depression (two cases), cup depression (eight cases), and saucer depression (six cases). The radiological findings were characteristic for each group. In the presence of funnel depression which is the most marked deformity, the heart was displaced bodily to the left of the spine and was unchanged in size or shape. In the cases of cup depression, the cardiac silhouette in the anterior view was less dense than normal and was moderately enlarged with prominence of the pulmonary arc. In the left oblique view, the heart shadow was normal or small and was displaced backward to overlap the spine, thereby obliterating the clear areas of the aortic window and the

retrocardiac space. Similar effects, although less in degree, were observed in the saucer depression. The importance of this last group is that the chest deformity is less obvious, and the changes to which it gives rise lead to erroneous interpretation of the enlarged cardiac area seen on radioscopy if the effects of the saucer depression are not fully appreciated. None of the sixteen patients had any actual enlargement of the heart or suffered symptoms related to the heart. All were healthy and were handicapped only by the restrictions imposed on them by a medical examination that had misinterpreted the clinical and radiological signs. LAPLACE.

Denolin, H.: The Electrocardiographic Criteria and Localization of Bundle Branch Block. The Present State of the Question. Acta Cardiologica **1**: 44, 1946.

The present concept of bundle branch block is reviewed. The author believes that none of the usually proposed electrocardiographic criteria can be accepted as wholly reliable to establish a diagnosis of this lesion or particularly of ventricular asynchronism. He considers it impossible to locate the site of an intraventricular conduction defect on the basis of the classic electrocardiogram because of the number of factors which modify the electrical picture, including the situation of the heart in the thorax, intrathoracic contacts, and associated myocardial damage. He states that only a demonstration of asynchronism of electrical or dynamic phenomena can warrant a diagnosis of bundle branch block and its localization. It is suggested that the term "disturbance of interventricular conduction" should be used rather than bundle branch block because ordinarily the available diagnostic criteria comprise simply the electrocardiographic pattern and give no indication of the functional activity of the ventricles. Further study of ventricular asynchronism in patients who have bundle branch block and curves of axis deviation is required. LAPLACE.

Priest, W. S., and McGee, C. S.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis. J. A. M. A. **132**:124 (Sept. 21), 1946.

In the treatment of subacute bacterial endocarditis with penicillin, these authors encountered four organisms which were highly or completely resistant to penicillin. One of these was the *Hemophilus parainfluenzae;* the other three organisms were streptococci. The *H. parainfluenzae* was apparently unaffected after many weeks of penicillin therapy in daily dosage up to 2 million units. Sulfamerazine also had no apparent effect in vitro. Cure resulted from the combined administration of penicillin in daily dosage of 500,000 to 1 million units and sulfamerazine in dosage sufficient to give a level in the blood of 0.8 to 11 mg. per cubic centimeter. The organism in this case was subsequently found to be sensitive in vitro to streptomycin. In a group of thirty-four patients, three strains of streptococci were encountered which were highly insensitive to penicillin. One was typically Streptococcus viridans after freezing but was rather atypical in primary cultures of blood. The other two were typical nonhemolytic streptococci.

In vitro sensitivity to penicillin ranged from 0.8 to 6 units per cubic centimeter. Sensitivity to streptomycin ranged from 0.1 to 1 unit per cubic centimeter. Streptomycin apparently produced sterilization of the valvular lesions in Case I, resulted in negative cultures of blood after penicillin therapy had failed in Case II, and was solely responsible for the cure obtained in Case III.

The dose of streptomycin used, 500,000 units (0.5 Gm.) per day, is not necessarily that which will be adequate in all cases in which use of the drug is indicated. BELLET.

Gross, R. E., and Ware, P. F.: The Surgical Significance of Aortic Arch Anomalies. Surg., Gynec. & Obst. **83**:435 (Oct.), 1946.

A brief resume is made of the more common anomalies of the aortic arch and the large arteries which arise from it. Many of the anomalies do not produce important symptoms, but others have considerable significance since they give rise to pressure on the esophagus and trachea, impose a burden on the heart because of an arteriovenous type of shunt, or lead to severe derangements in the circulation because of an obstruction in the aortic pathway.

In the first group of malformations the esophagus or trachea (or both) are impinged upon by (1) a right-sided aortic arch, (2) a double aortic arch, (3) a constricting ring of vessels (or remnants

thereof), or (4) an anomalous right subclavian artery. A right-sided aortic arch cannot be changed by surgical means, but if this abnormally placed structure is attached by a ligamentum arteriosum (or a patent ductus arteriosus) to the pulmonary artery so that this latter vessel is pulled back against the trachea on the left side of the esophagus, then division of the ligament (or of the ductus) should give some relief. When a double (or split) aortic arch gives respiratory distress, the patient can be greatly helped by cutting the anterior (left) limb. When dysphagia occurs from a right subclavian artery, which originates from the left side of the aortic arch, the symptoms can be abolished by dividing the artery so that it no longer presses on the esophagus.

While some individuals live a long and active life with a patent ductus arteriosus, particularly if it is a small one, statistics indicate that the average length of life is little more than half of the normal expectancy. While surgery can be deferred until symptoms have developed, the technical difficulties of operation at such times are considerable. In contrast, the closure of a ductus at an early age can be accomplished with a negligible risk, and hence operation is recommended in childhood or young adult life before complications have developed. Experience indicates that ligation of a ductus is usually satisfactory but that complete division of the vessel is more desirable because it insures complete interruption of the shunt and precludes any possibility of its re-establishment.

Individuals with a high degree of obstruction in the distal part of the aortic arch or in the first part of the descending aorta may live to advanced ages with little or no difficulty, but most of them develop serious or even fatal complications in mid-life, particularly hypertension with its sequelae. Experimental observations show that a section of the upper thoracic aorta can be excised and that the open ends of the aorta can be satisfactorily joined. Such a procedure has been adapted to human beings; a narrowed (or completely obstructed) segment of the aorta can be removed and the remaining ends of the aorta can be anastomosed. After performance of this operation, the hypertension is quickly relieved. Five patients with coarctation of the aorta have been operated upon with only one death. The fatality occurred in the first patient in whom the clamps were removed from the vessel too quickly, before adjustments could be made in the cardiovascular apparatus to the opening up of an enormous vascular bed in the lower part of the body.

NAIDE.

Dick, G. F., and Schwartz, W. B.: Experimental Endocarditis of Dogs. Arch Path. **42**:159 (Aug.), 1946.

The authors studied the incidence of experimental endocarditis in dogs, with special reference to the type of the organism, its virulence, and its dosage. Intravenous injections four times weekly of cultures fortified by the addition of sterile dog blood resulted in the development of bacterial endocarditis in 61 per cent of twenty-six dogs. The organisms were various strains of *Streptococcus hemolyticus* and *Streptococcus viridans* isolated from the blood and urine of human patients. Beta hemolytic and viridans strains produced positive results with equal frequency and, contrary to existing opinion, previous damage to the heart valves was not essential. It was not necessary that the streptococci should come from human endocarditis; similar organisms from a great variety of human lesions were used with equal success. Organisms other than streptococci did not induce endocarditis in these dogs.

GOULEY.

Barnes, A. C., and Ervin, H. K.: The Effect of the Anticoagulants on Postpartum Bleeding. Surg., Gynec., & Obst. **83**:528 (Oct.), 1946.

This study was undertaken to determine whether or not anticoagulants are contraindicated by vaginal bleeding post partum. Eleven patients who served as controls uniformly showed the marked elevation of prothrombin level which has been noted in a normal postpartum patient. Readings as high as 130 per cent were obtained (second day following delivery), and with the exception of one reading of 85 per cent on the third postpartum day, the hemoglobin did not fall below 100 per cent in any patient until after the fifth day. Fourteen postpartum patients were given dicumarol in doses adequate to depress their prothrombin levels to the therapeutic range. Five postpartum patients were given heparin in therapeutic doses.

Although the present series is not large, the patients were followed carefully and the authors were unable to find evidence that anticoagulants significantly increased peripheral blood loss. The customary precautions in connection with the use of these drugs should be scrupulously observed. The data obtained would indicate that heparin and dicumarol are not necessarily contraindicated in the postpartum patient. Although the blood loss in these patients was the same as that of the controls, two of them with episiotomy wounds developed hematomas, and one of these patients underwent a partial breakdown. Aside from this complication, the treated patients presented the same findings as did the control group.

Bleeding and clotting times obtained on the nursing babies showed prolongation in over one-third of the cases. These reactions were not consistent: in two cases, both were prolonged. In the other three, only the clotting time was increased. It is felt that these studies performed on toe or heel blood are not sufficiently delicate for the results to bear close scrutiny. In view of the report by Field, however, that rat litters nursed by dicumarolized females showed hemorrhagic tendencies, it might be wise to consider weaning a baby whose mother required prolonged medication with dicumarol. NAIDE.

Shumacker, H. B.: The Surgical Treatment of Gangrene in Trench Foot. Surg., Gynec., & Obst. **83**:513 (Oct.), 1946.

Superficial gangrene in trench foot does not present a serious problem. However, the great majority of patients with deep gangrene have infection of a mixed character. Although such infection is often controlled satisfactorily with sulfadiazine or penicillin and with the local application of warm saline compresses following the removal of gangrenous parts, organisms resistant to these drugs are commonly present.

Vasoconstriction, sometimes intense, was present in the majority of patients. It is thought that lumbar sympathetic ganglionectomy is a useful adjunct in the treatment of deep gangrene of trench foot and that it results in more speedy healing and in conservation of tissue. In the event that skin defects have resulted from the loss of parts, it is advisable to cover these areas with a split thickness or full thickness graft. If the ends of metatarsals are exposed, a graft of full thickness is generally necessary. The stump is satisfactory for standing or walking, if all the toes are removed, or even if parts of the metatarsal heads must be removed. If amputation must be carried out more proximally through the metatarsals, the stump is generally unsatisfactory. Pain on weight-bearing was not peculiar to the patients who had undergone amputations but occurred just as frequently in patients with trench foot who had had no gangrene at all.

NAIDE.

Kahn, J. W.: Thrombophlebitis of the Deep Veins in Thromboangiitis Obliterans. Surg., Gynec. & Obst. **83**:449 (Oct.), 1946.

Two patients with thromboangiitis obliterans are reported in whom deep thrombophlebitis was the presenting symptom. One of the patients developed pulmonary infarction secondary to the thrombophlebitis. This is a rare complication in thromboangiitis obliterans. The arterial tree should be carefully investigated in all cases of afebrile, idiopathic, deep thrombophlebitis in young patients. The presence of passive congestion in a limb secondary to venous obstruction may cause a reactive hyperemia which temporarily may mask some of the signs and symptoms of arterial insufficiency. NAIDE.

Berry, R. L., Campbell, K. N., Lyons, R. H., Moe, J. K., and Sutler, M. R.: The Use of Tetraethylammonium in Peripheral Vascular Disease and Causalgic States. Surgery **20**: 525 (Oct.), 1946.

A new method of producing a blockade of autonomic ganglia by means of parenteral injection of tetraethylammonium bromide or chloride is reported. Acheson and Moe studied the action of tetraethylammonium and concluded that the responses of the nictitating membrane, the blood pressure, and the heart rate could all be explained by a blockade of autonomic ganglia, both sympathetic and parasympathetic.

In the present report, the results of the use of this compound in a variety of peripheral vascular diseases and causalgic states is described. The drug is administered intravenously or intramuscularly. The intravenous dose ranged from 100 to 500 mg. This was injected slowly in from fifteen to sixty seconds; significant changes in the volume of the pulse and the general reaction of the patient were used as guides to cease or delay further administration of the drug. Intramuscular injections were utilized to prolong the effect of the autonomic blockade only in patients under observation in the hospital. These were given in doses of less than 20 mg. per kilogram of body weight, 1.0 to 1.5 Gm., one-half the dose being administered in each buttock.

The intravenous administration produces a metallic taste in fifteen to twenty seconds and is followed by a sense of numbness and tingling in the extremities which is associated usually with a fall in blood pressure in hypertensive patients and a rise in heart rate. Sweating, if present, stops, the mouth becomes dry, and there is incomplete dilatation of the pupil with loss of accommodation. With the fall in blood pressure, there is an increase in skin temperature of the toes and fingers, usually within five minutes, which persists after the blood pressure returns to its initial level. Though the blood pressure in the supine position returns to its initial level, postural hypotension may exist in diminishing intensity for fifteen to sixty minutes. The vasoconstriction gradient is largely abolished so that the toe and thigh temperatures are equalized.

The effects of tetraethylammonium on peripheral blood flow were compared with the effects of lumbar sympathetic blocks, spinal anesthesia, local nerve block, and sympathectomy. This comparison was made both in patients with vascular disease and in a control group of relatively healthy individuals. In fifty-two of fifty-five comparative tests, tetraethylammonium proved equal or superior to the usually accepted methods of producing sympathetic block. The ease of administration is an additional highly desirable feature of tetraethylammonium, since spinal anesthesia is not always desirable or possible and paravertebral sympathetic block, even in expert hands, is not always successful.

Approximately 500 patients received tetraethylammonium bromide or chloride on one or more occasions, either as a diagnostic or therapeutic measure or both. The various diseases studied included hypertension, arteriosclerosis obliterans, thromboangiitis obliterans, Raynaud's syndrome, livedo reticularis, acrocyanosis, causalgic states including various types of reflex sympathetic dystrophy, superficial and deep thrombophlebitis with and without evidence of vasospasm, various types of lymphedema, post-traumatic edema, scleroderma, endarteritis, herpes zoster and post-herpetic neuralgias, and trench and immersion foot sequelae.

Tetraethylammonium has proved to be a satisfactory method of producing either a temporary or prolonged sympathetic block and is therefore useful in improving the circulation or ameliorating pain of circulatory origin.

The intravenous injection of this drug to produce autonomic blockade has been utilized daily as an outpatient procedure for eight months. No emergency hospitalization following the administration of this drug has been necessitated at any time. The patient is asked to refrain from driving his car from one to two hours because of loss of accommodation. The patient is usually unaware of any visual impairment. Adrenalin is specific in counteracting any untoward symptoms.

In the doses used in this study and in the patients reported here, no significant toxic effects were noted. In other cases reported elsewhere, complications of the injection were experienced. Some patients with very high blood pressure experienced a state of peripheral circulatory collapse following the intravenous injection which was quite transient in character and which responded to epinephrine. Other patients developed a state of dyspnea similar to that observed in hysterical hyperventilation. In a few patients, the sensations of weakness, fatigue, and lightheadedness were very pronounced. The drug has been administered more than one thousand times to more than 500 patients in the doses indicated with very few alarming reactions.

NAIDE.

Chambers, William N.: Acute Myocardial Infarction. New England J. Med. **235**:347 (Sept. 12), 1946.

The author observed 100 consecutive patients in their initial attack of acute myocardial infarction. Thirty-four patients died within the first thirty days, and an additional eight died

within one year. The average age of the 100 patients was 59 years; the average age of those who died was three years greater than of those who survived. The ratio of men to women was 3 to 1. The women of these series were older and had a higher mortality rate than the men. In eighty-four of the patients, dyspnea, anginal pain, or other symptoms of cardiovascular disease preceded the infarction. Hypertension was known to have existed in seventy-four of the patients and diabetes in thirteen. Pain, the most frequent symptom, occurred in seventy patients. Dyspnea, the second most prominent chief complaint, occurred in twenty-six patients. The most frequent physical findings were poor heart sounds and congestive râles, cyanosis, edema, tachycardia fever, and disturbances in rhythm. These and other physical signs were considerably more prominent in those who died in the initial attack than in those who survived. Congestive heart failure was present on admission or subsequently developed in 65 per cent of the fatal cases. Pulmonary embolism occurred in six patients, five of whom survived. Cerebral hemorrhage resulted in death in one of the two patients in whom it developed. Other thrombotic or embolic complications are not described. Variations of blood pressure and of the leucocyte counts and sedimentation rates are described and correlated with mortality. Electrocardiographic tracings indicated anterior-apex infarctions in fifty-two patients, posterior-base infarctions in forty, and a combination of types in eight. Three months after the infarction, none of the tracings had returned to normal; after two years, thirty-eight patients had normal tracings.

Of the fifty-eight patients who survived one year, nine had had nonfatal recurrent infarctions, Of the other forty-nine, half had angina pectoris, eight had some symptom of cardiac insufficiency. and eleven were without symptoms. About half of these patients were working full or part time.

KAY.

Brun, C., Knudsen, E. O. E., and Raaschou, F.: Kidney Function and Circulatory Collapse. Post-Syncopal Oliguria. J. Clin. Investigation **25**:568 (July), 1946.

Circulatory collapse was induced in healthy, water-loaded subjects by placing them in the passive erect posture on a tilt table at an angle of 40 to 60 degrees with the horizontal plane. After symptoms and signs of collapse appeared, the subjects were returned to the horizontal position with immediate restoration of the circulation to normal, as judged by the pulse, blood pressure, and subjective symptoms. Hematocrit, blood viscosity, and plasma proteins increased to levels above control values as the passive erect position was maintained, but no conspicuous changes in urine flow were observed until collapse intervened. Oliguria then occurred and persisted fifteen to ninety minutes after the subjects were returned to the horizontal position. During the period of post-syncopal oliguria, urinary specific gravity rose from low values to 1.020 to 1.025, and the hematocrit, blood viscosity, and plasma proteins gradually returned to control levels. In the immediate post-syncopal period, inulin clearance (glomerular filtration rate) and diodrast clearance (effective renal plasma flow) were reduced to 70 and 75 per cent, respectively, of their control values but for only a fraction of the total period of oliguria.

The absence of persistent reduction in glomerular filtration suggested that the oliguria was due to the presence in the circulating blood of an antidiuretic substance which caused increased reabsorption of water by the renal tubules. This hypothesis was examined by transfusing into water-loaded, supine subjects heparinized blood obtained from post-syncopal donors. The post-transfusion oliguria obtained lasted thirty to forty-seven minutes and was accompanied by increased concentration of urinary chloride. Blood obtained from control subjects exerted no similar effect, but the administration of five international units of posterior pituitary substance reproduced the oliguria and the increased urinary chloride concentration, and further resembled post-syncopal oliguria in that total urinary chloride tended to diminish somewhat.

The reduced output of total urinary chloride observed in these experiments was not in accord with the results of other investigators but the authors explained this discrepancy on the basis of prior negative chloride balance induced in their subjects by the water diuresis.

Two patients with diabetes insipidus developed distinctly less prolonged post-syncopal oliguria and it was postulated that these individuals possessed less ability to produce antidiuretic hormone.

It is intimated that the effective stimulus for the secretion of antidiuretic hormone may be either cerebral anoxia or reflexes mediated through the pressor receptors. It is also suggested

that the oliguria seen in other types of circulatory insufficiency, such as cardiac insufficiency, diabetic coma, and shock, may be associated with this mechanism. FRIEDLAND.

Ogura, J. H., Fetter, N. R., Blankenhorn, M. A., and Glueck, H. I.: Changes in Blood Coagulation Following Coronary Thrombosis Measured by the Heparin Retarded Clotting Test (Waugh and Ruddick Test). J. Clin. Investigation **25**:586 (July), 1946.

This study was motivated by a previous study in which one of the authors found auricular or ventricular mural thrombi in 65 of 100 cases of coronary thrombosis which were studied post mortem. The Waugh-Ruddick technique was applied to the blood of patients admitted to the hospital with unquestionable findings of coronary thrombosis. The technique consists of recording and plotting the coagulation time of blood in a series of nine tubes to which increasing quantities of heparin are added. With coagulation time plotted on the ordinate and tube number on the abscissa, an acceleration is demonstrated by "flattening of the curve," i. e., the greater the blood's coagulability, the faster the coagulation time. In the tube (No. 9) containing the largest quantity (7/10 unit) of heparin, the coagulation is slowest; small differences in coagulation time are magnified.

Twenty-one of twenty-seven patients with coronary thrombosis were found to have accelerated coagulation commonly by the third day and usually by the twelfth day. In twenty-three there was a return to normal by the end of the third week.

Control patients showed some acceleration of coagulation after their third day in bed, but the acceleration was not as pronounced as it was in patients with coronary thrombosis. There is a suggestion that thrombo-embolic complications may be associated with acceleration of coagulation. In six patients with coronary thrombosis who were receiving digitalis, the data do not suggest that digitalis accelerates coagulation. Neither did xanthines influence the coagulation curve.

In view of the delay in the acceleration of coagulation until the second or third day after the onset of coronary thrombosis, the data indicate that accelerated coagulability is not a cause of coronary thrombosis but is rather a result of the thrombosis and the possible release of thromboplastin by the subsequent tissue damage.

It would appear that early anticoagulant therapy may prevent the formation of mural thrombi and the subsequent embolic phenomena. FRIEDLAND.

Bedford, D. E., Aidaros, S. M., and Girgis, B.: Bilharzial Heart Disease in Egypt. Brit. Heart J. **8**:87 (April), 1946.

Corpulmonale with gross dilatation of the pulmonary artery is by no means rare in Egypt and is usually encountered in young adults suffering from advanced visceral bilharziasis or from severe genito-urinary infection with *Schistosoma hematobium*. A case of "Bilharzial Ayerza's disease" is reported because, in spite of the frequency of this condition in Egypt, the number of cases on record is scanty. The patient, a 34-year-old farmer, was admitted to Kasr-el-Aini Hospital, Cairo, complaining of dyspnea on exertion, productive cough, and precordial pain of three years' duration. Examination revealed cardiac enlargement but no manifestations of congestive failure other than mild dyspnea. An x-ray film showed great enlargement of the pulmonary artery. Three weeks after admission, he began to have acute congestive failure and died within a few days. Autopsy revealed pulmonary endarteritis due to bilharziasis; atheroma and aneurysmal dilatation of the pulmonary artery and minor branches; hypertrophy and dilatation of the right heart; cirrhosis of the liver; biharzial splenomegal and bilharzial cystitis.

This disease affects young adults infected with *Schistosoma mansoni* or *S. hemaiobium* or both. Cyanosis and clubbing of the fingers are relatively slight and clinical, and radiological signs of lung disease are slight or absent. Dilatation of the pulmonary artery may amount to aneurysm and relative pulmonary incompetence is common. The x-ray appearance of the heart is similar to that of atrial septal defect. Pathologically, the changes consist mainly of an obliterative pulmonary endarteritis. Histologically bilharzia ova are found in the walls of the small vessels and in extravascular tubercles. In the later stages, the occluded vessels become expanded by highly vascularized tissue to form "angeiomatoids," which are a distinctive feature of bilharzial arteritis. LAPLACE.

Book Reviews

CLINICAL ROENTGENOLOGY OF THE HEART. By John B. Schwedel, M.D. Annals of Roentgenology, Vol. XVIII, New York, 1946, Paul B. Hoeber, Inc.

In his preface, the author justifies the writing of a new medical book only on the bases of "original contributions or simplicity of presentation or . . . . the further development of thesis not fully exploited methods. . . . ." In the opinion of the reviewer, he has justified his thesis by fulfilling the second requirement. His descriptive material is clearly presented and is rarely of a controversial character. The very numerous roentgenograms were carefully selected and are of uniformly high technical quality and of sufficient size to make important details easily visible. The diagrams, paired with most of the roentgenograms, are more clearly and quickly explanatory than the usual legends. The addition of a chapter on the lungs in heart disease is welcome and indispensable in a work of this kind. The format of the volume is excellent.

Few adverse criticisms can be offered. It is inevitable that in a first edition of a book with many illustrations some of them will be inverted and others reversed. The book will be chiefly interesting to the roentgenologist and to the cardiologist; the latter would probably prefer more clinical data in the legends, and also more electrocardiograms when these are pertinent and helpful in the diagnosis. This applies particularly to the subject of congenital heart defects, which deserves a somewhat fuller treatment. . . . . The valuable contributions of the method of contrast visualization are insufficiently presented. On page 73 appears this statement: "The criterion for left ventricular rounding and enlargement is fulfilled when the arc of the left ventricular segment, if extended, forms a circle, the projected outline of which does not fall beyond the confines of the fluoroscopic screen or the x-ray film. If the circle thus formed is large and extends beyond the fluoroscopic screen, the left ventricle is less likely to be enlarged." (Rule of the circle.) This attempt to draw a relation between the size of the left ventricle and the size of a fluoroscopic screen or x-ray film appears to us to be unscientific. The clinical value of the differentiation of ventricular enlargement into outflow and inflow tract enlargements is not convincingly established. Furthermore, the determination of the lengths of the inflow tracts depends on the accurate localizations, in the left anterior oblique view, of the junction of the left auricular border with that of the left ventricle, and also of the position of the interventricular groove. These localizations are usually difficult, frequently impossible, and almost always uncertain.

Despite these criticisms, the novice and expert, alike, will read this book with considerable pleasure and profit, and it is highly recommended.

A. MARGOLIES, M.D.

NORDISK LAEREBOG I INTERN MEDICIN Vol. IV. Circulatory Diseases. By Erik Warburg, Copenhagen, Gyldenalske, Boghandel, Nordisk Forlag, Copenhagen, 1946, 366 pages.

This volume is part of the standard textbook in internal medicine which is used at the medical schools in Scandinavia. The book is divided into three parts. Part one deals with general aspects of cardiology: pathologic physiology of the cardiovascular system, the mechanism and clinical aspects of myocardial insufficiency, and diagnostic methods. Part two is concerned with the various forms of heart disease; many uncommon conditions are considered. Special sections are given over to the discussion of pregnancy, sport, and surgery in relation to the heart, and to the use of digitalis. The last part, about one-fifth of the book, is devoted to the discussion of diseases of the arteries.

The style is clear, concise, and, of necessity, somewhat didactic, and the book appears readable even to those with but limited knowledge of Scandinavian languages. The author is well oriented in American literature and for its content matter it might well be placed in the hands of American students.

In three respects it is also of interest to advanced students. Its pathophysiologic approach to the field is novel to modern books, though reminiscent of Hirschfelder. It contains many historical references which are not commonly found in American texts: for instance, he refers to Malmsten's diagnosis in vivo of myocardial infarction in 1859 (confirmed by autopsy), to Payne-Cotton's (1869) and Probstrings' (1882) descriptions of paroxysmal tachycardia, and to Winge and Heiberg's demonstration in 1869 of bacteria in the heart valves which were the site of bacterial endocarditis, and to Jaccond's description of the same disease in 1885. Finally the author has incorporated a great many contributions by Scandinavian workers who have received scant recognition in this country; many of these contributions are theses which contain a great deal of valuable observations. Therefore, the book would be of very great value if it were not for one serious defect: it has no bibliography. While informing the reader of the existence of many valuable contributions, it does not direct him to them. Inasmuch as many of these are theses or are found in Scandinavian publications of limited circulation they may be difficult of acccess to American readers. It is hoped that this defect may be remedied in future editions.

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THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

Annual membership in the American Heart Association is $2.50 and includes twelve issues of *Modern Concepts of Cardiovascular Disease;* Journal membership is $10.00 and includes a year's subscription to the American Heart Journal (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease*, and annual membership in the Association. Contributing membership starts at $25.00 per year; patron membership is $50.00 and over per year. Membership blanks will be sent upon request.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

Annual Meeting

The Annual Meeting and Twentieth Scientific Sessions of the American Heart Association will be held in Atlantic City, N. J., June 6 and 7, 1947. The Hotel President will be the headquarters for all meetings. On June 6, a meeting will be held with representatives of local Heart Associations to discuss the administrative structure of the American Heart Association with particular reference to program. The annual meeting of members will also be held on that day. The scientific sessions will take place on June 6 and 7. The annual dinner is scheduled for Saturday evening, June 7, at the Hotel President. Meetings begin at 9:00 A.M. each day, and members should plan to arrive on June 5. Hotel rooms will be in great demand and every member who wishes to attend is urged to make reservations immediately.

The chairman of the Program Committee for the Annual Scientific Sessions of the American Heart Association is Dr. Edgar V. Allen, Mayo Clinic, Rochester, Minn. All who desire to present papers at the meetings of June 6 and 7 in Atlantic City should forward to him an abstract of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is March 30, 1947.